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THE UNIVERSITY OF ALBERTA

# SYNTHETIC STUDIES ON DENDROBINE AND ISOACANTHODORAL

BY

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1986

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submitted by L. A. K. NELSON in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

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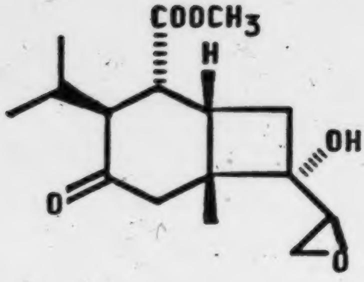
# ABSTRACT

Chapter one of this thesis describes the preparation of the epoxy alcohol I, a potential intermediate towards the total synthesis of dendrobine II, from piperitone III. Photocycloaddition between piperitone III and vinyl acetate gave the adduct IV after base treatment. Hydrolysis of the acetate IV with potassium carbonate in aqueous methanol followed by Swern oxidation of the resulting alcohol gave the chloro diketone V. Dehydrochlorination of V with a mixture of chlorotrimethylsilane and triethylamine in dimethylformamide gave the enone VI. Selective ketalization of the cyclobutanone moiety with 2-ethyl-2-methyl-1,3-dioxolane in the presence of *p*-toluenesulfonic acid followed by reduction of the enone ketone with sodium borohydride gave the allylic alcohol VII. Methylation of the hydroxyl group with methyl iodide followed by treatment of the allylic ether sequentially with diborane, basic hydrogen peroxide and pyridinium dichromate gave the ketone VIII. Elimination of methanol from VIII with 1,8-diazabicyclo[5.4.0]undec-7-ene gave the enone IX. A 1,4-addition of lithium divinylcuprate to IX, followed by ruthenium tetroxide cleavage of the carbon-carbon double bond and methylation of the resulting



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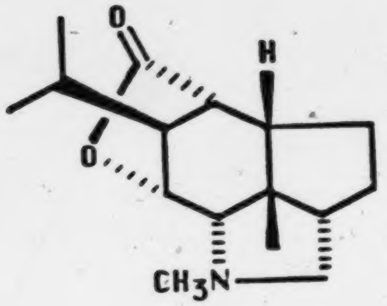

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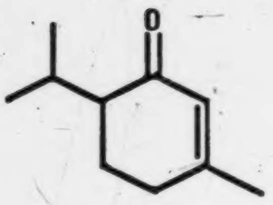

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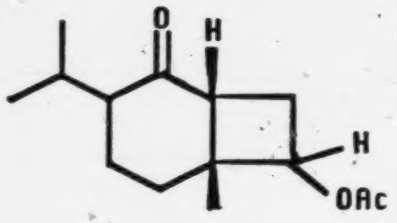

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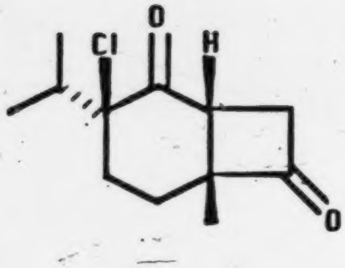

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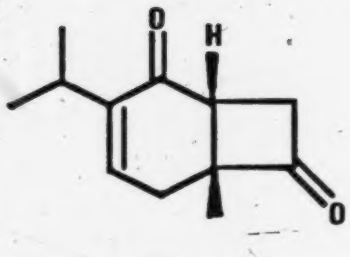

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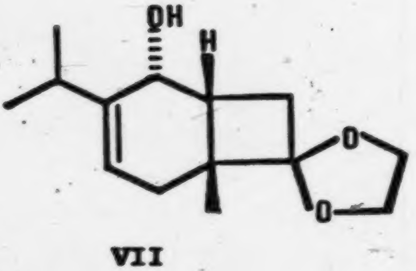

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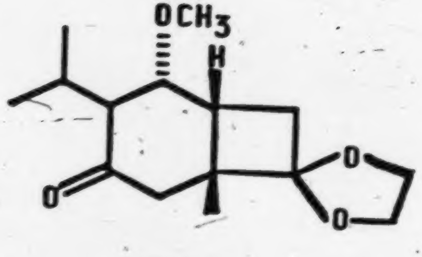

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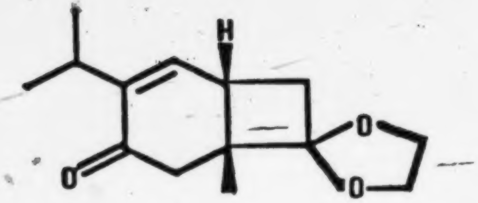

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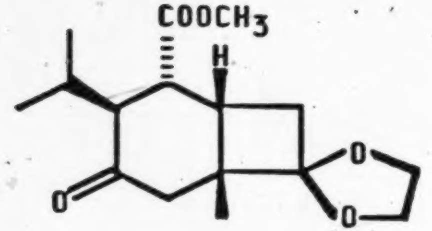

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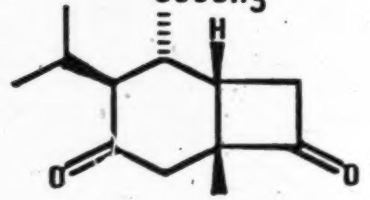
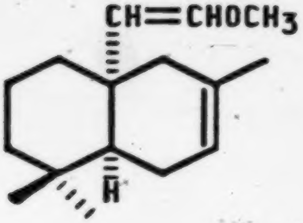


XI

carboxylic acid with potassium carbonate and methyl iodide gave the keto ester X.

Deprotection of the cyclobutatanone moiety with p-toluenesulfonic acid in acetone yielded the diketo ester XI. Vinyllithium addition to the four-membered ring ketone followed by epoxidation of the carbon-carbon double bond with m-chloroperbenzoic acid gave the epoxy alcohol I.

The second chapter describes the preparation of the enol ether XII, a potential intermediate towards the synthesis of isoacanthodoral XIII, starting from 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadienone XIV. Diels-Alder reaction of XIV with isoprene in the presence of boron trifluoride etherate gave the 1:1 adduct XV. Reduction of the enone carbon-carbon double bond with Wilkinson's catalyst in triethylsilane followed by hydrolysis of the resulting enol silyl ether with potassium carbonate in methanol gave the saturated ketone XVI. Reduction of the saturated ketone with sodium borohydride to an alcohol, followed by conversion of the alcohol to xanthate XVII with carbon disulfide, methyl iodide, and sodium hydride and treatment of the xanthate XVII with tri-n-butyltin hydride in the presence of 2,2'-azobis(2-methyl-2-propionitrile) gave the ester XVIII. The ester XVIII was reduced to an alcohol with sodium bis-



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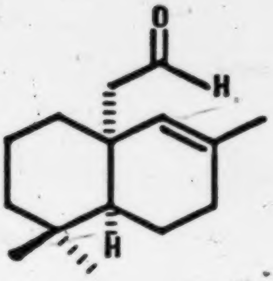

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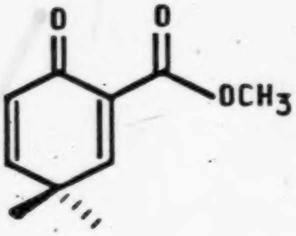

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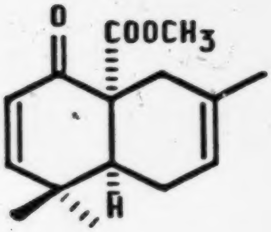

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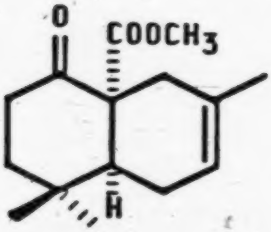

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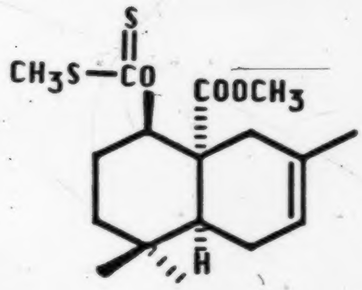

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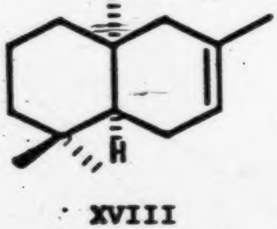

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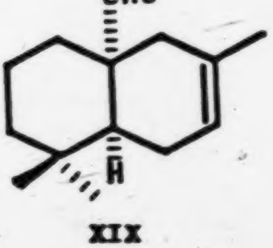

XIX

(2-methoxyethoxy)aluminum hydride and the resulting alcohol oxidized by Swern's oxidation to the aldehyde XIX.

Wittig reaction of the aldehyde XIX with (methoxymethyl)triphenylphosphorane ylide gave the enol ether XII.

# ACKNOWLEDGEMENTS

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# CHAPTER I

# SYNTHETIC STUDIES ON DENDROBINE

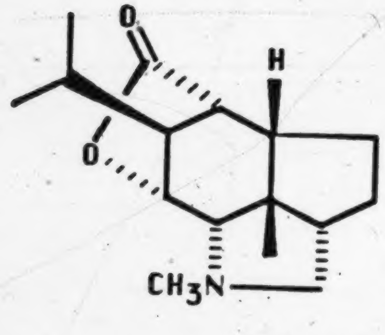
# INTRODUCTION

Dendrobine (**1**) is the major alkaloid constituent of a Chinese herbal preparation, "Chin Shih Hu", which has been used for centuries as a tonic and antipyretic. The species responsible for the alkaloid content of this preparation is the ornamental orchid, *Dendrobium nobile* Lindl. which belongs to the family *Orchidaceae*.

Dendrobine (**1**) was the first alkaloid isolated from *Dendrobium nobile* Lindl. in 1932 by Suzuki, *et al*.[1,2] They also revealed its molecular formula, the presence of an *N*-methyl group and a lactone function. The complete structure was reported in 1964 by three independent groups.[3-5]

To date, a total of fourteen structurally related alkaloids have been isolated from *D. nobile* and other *Dendrobium* species.[6,7] Structures have been assigned to these alkaloids on the basis of extensive degradation studies, by chemical interconversions, and/or by spectroscopic methods.[6,7]

The absolute configuration of dendrobine (**1**) was established by circular dichroism studies on various members of the family.[8] Dendrobine (**1**) is structurally similar to the potent convulsant picrotoxinin (**2**). Both compounds contain the same basic elements of a bridging



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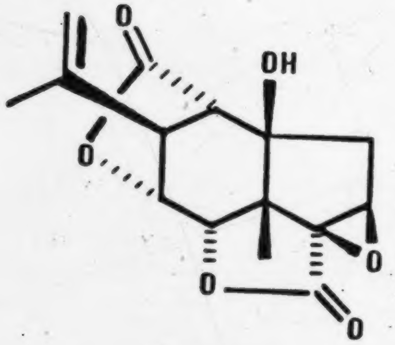

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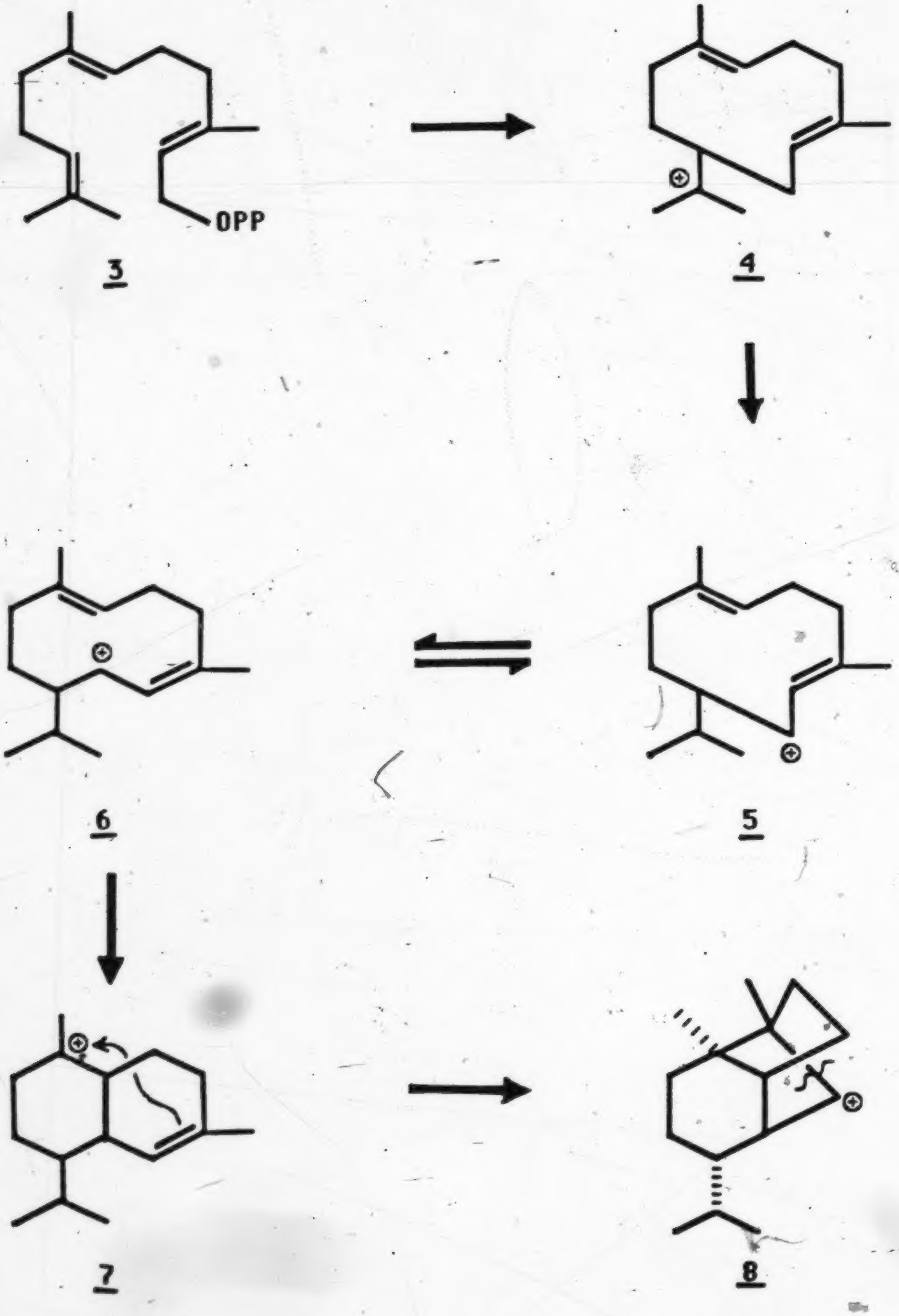
lactone and a hydrindane ring system to which a second heterocyclic ring is appended. These two compounds also share similar physiological properties - high mammalian toxicity, eventually causing death by convulsion.[6]

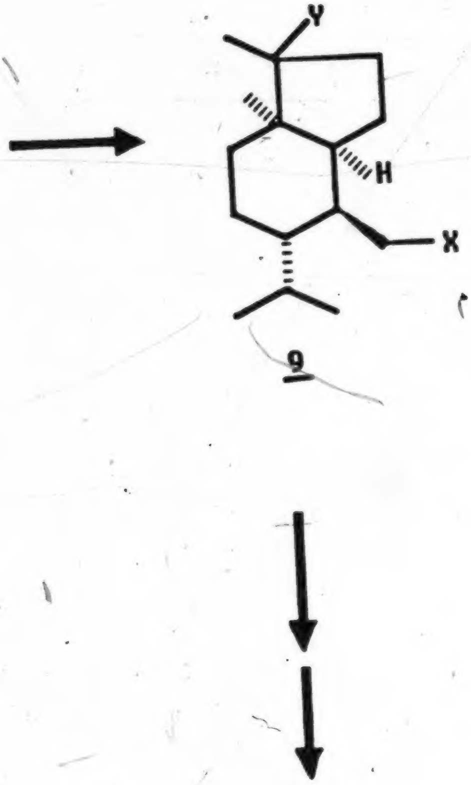
The early stages of the biosynthetic pathway of dendrobine have been studied.[9-11] 2-trans-6-trans-Farnesyl pyrophosphate (**3**) has been shown to be the precursor in the biosynthesis of dendrobine.[11] Thus, the intermediate 3 can cyclize to 4, which after a 1,3-hydride shift should give the germacrene intermediate 5 (Scheme I). A trans-cis double bond isomerization (**5** → **6**), followed by cyclization would give the muurolane cation **7**. An anti-Markovnikov addition of the double bond in **7** to the cation would give a tricyclic cation **8**. A carbon-carbon bond cleavage (as indicated) would give the hydrindane derivative **9** which would eventually lead to dendrobine (**1**).[12,13]

Due to their potent biological activity and unique polycyclic structures, picrotoxinin (**2**) and Dendrobine (**1**) have attracted considerable attention from synthetic chemists. To date, there have been three synthetic approaches to the dendrobine skeleton,[14-16] one synthesis of an epimer,[17] and four total syntheses.[18-21]

The first total synthesis of dendrobine (**1**) was reported by Yamada, et al[18] who used an intramolecular

## SCHEME I





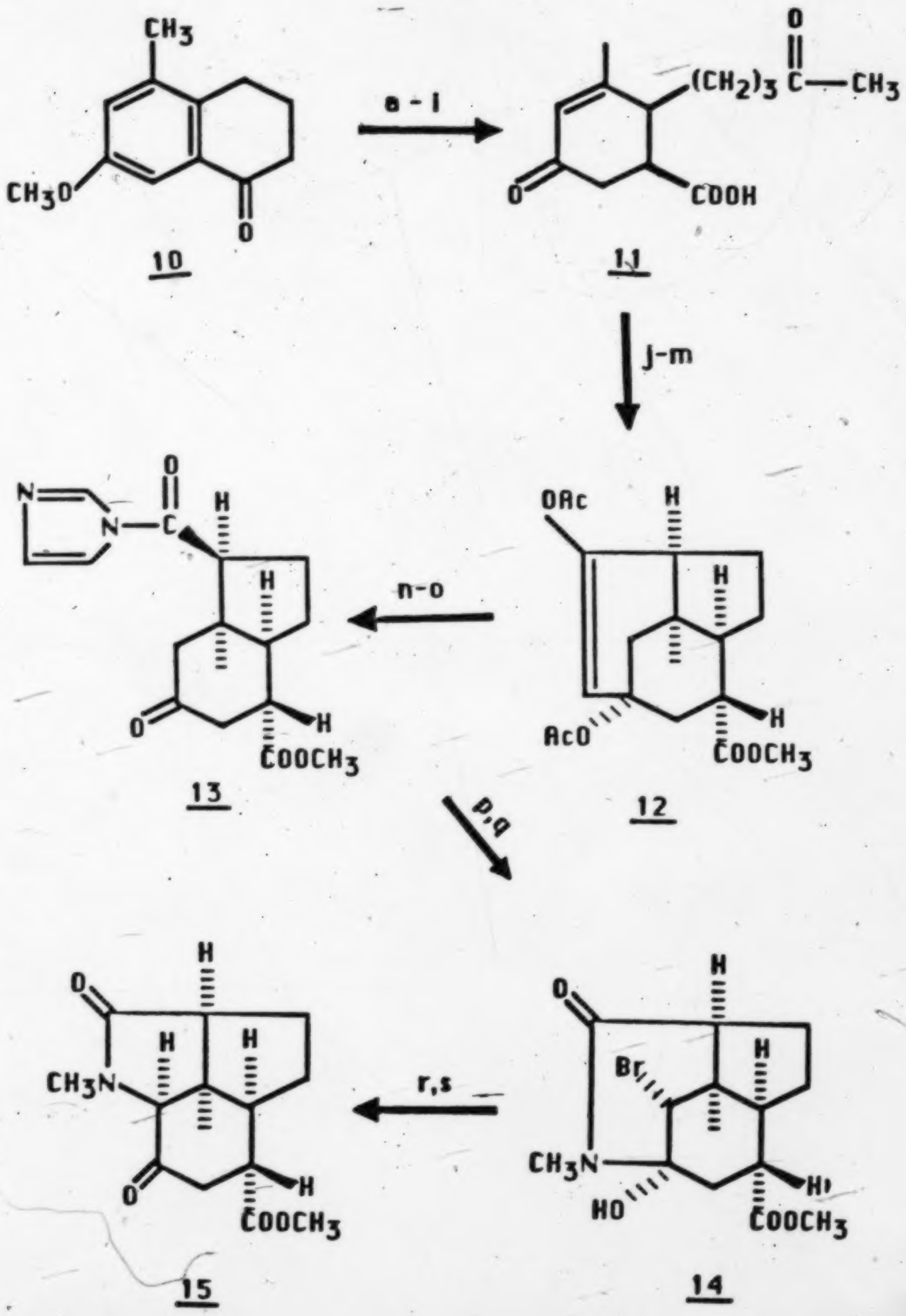
9

1

Michael reaction for the construction of the cis-hydrindane system as a key step. Thus, 3,4-dihydro-7-methoxy-5-methyl-1(2H)-naphthalenone (**10**) was elaborated into compound 11 in nine steps (Scheme II). An intramolecular Michael reaction on **11** using potassium tert-butoxide as base, followed by fractional recrystallization and functional group modifications gave the enol acetate **12**. The enol acetate **12** was converted, in two steps, to compound **13** which upon treatment with 40% aqueous methylamine-glyme (1:1) mixture, followed by bromination was converted to the lactam **14**. Treatment of **14** with sodium hydride in glyme followed by acidification gave **15**. Introduction of the isopropyl unit gave compound **16**. Sodium borohydride reduction of **16** and treatment of the resulting compound with triethyl oxonium fluoroborate gave ((±)-dendrobine (**1**).

Inubushi and co-workers[19] used the diketone **17** obtained by the Boyce's procedure. The diketone **17** was converted to keto nitrile **18** after a series of functional group manipulations (Scheme III). Bromination-dehydrobromination of the keto nitrile **18** afforded the enone **19**. Acid hydrolysis of the nitrile **19** afforded a carboxylic acid which underwent a concomitant intramolecular Michael reaction with the enone to give the lactone **20**. The lactone **20** was then converted to the

## SCHEME II


CH3
CH3O
O
10
a - i
O
(CH2)3 C—CH3
O
COOH
11
j-m
OAc
H
H
AcO
H
COOCH3
12
n-o
N
N—C
O
H
H
O
H
COOCH3
13
p,q
O
H
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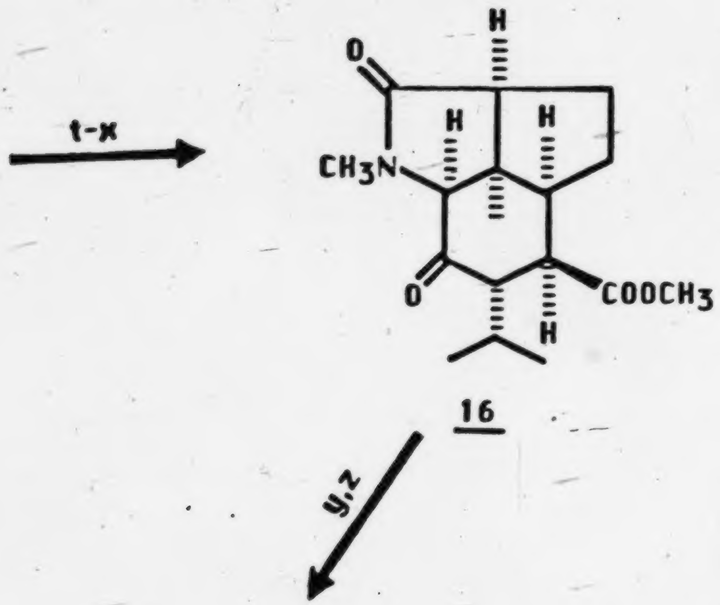
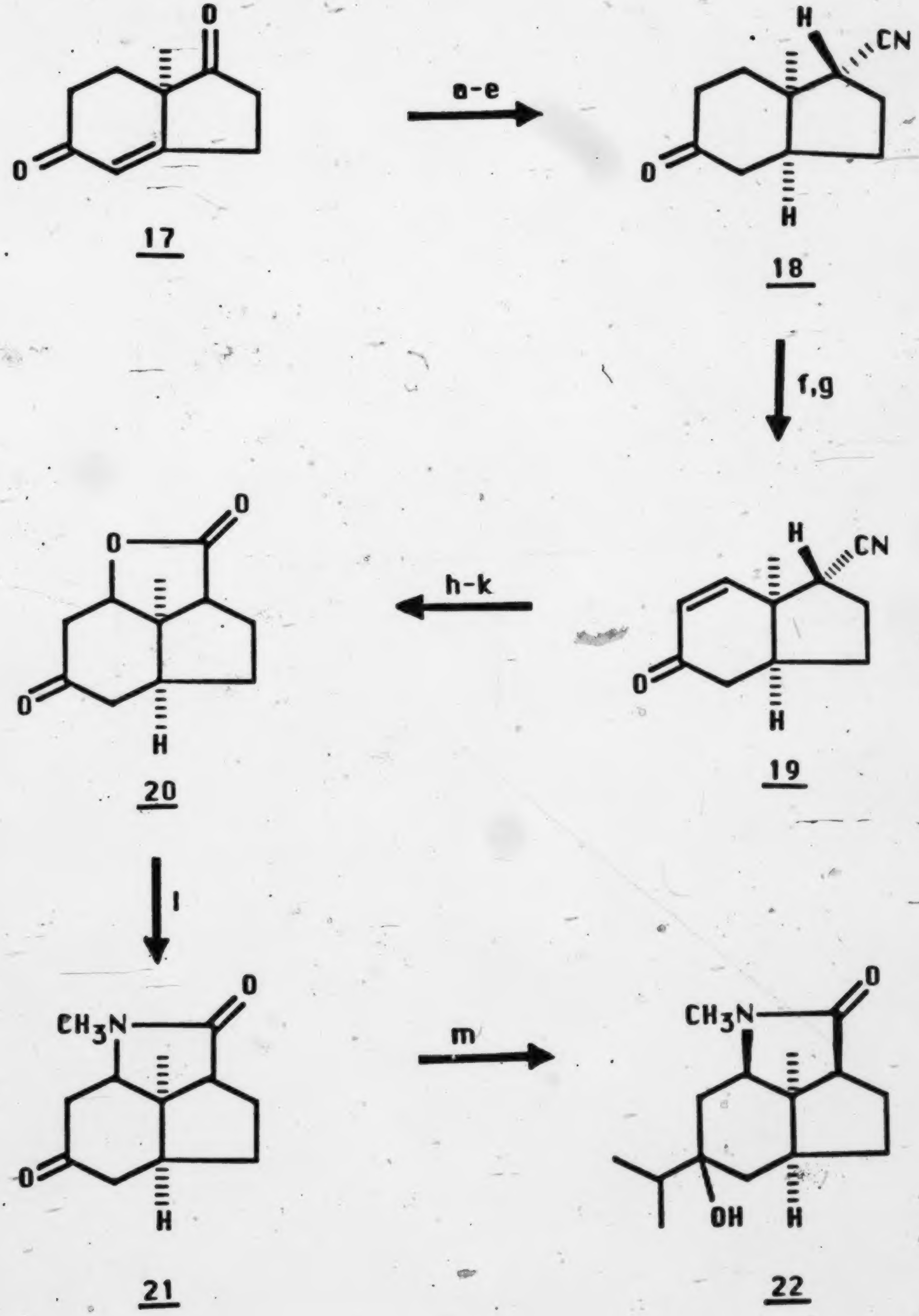


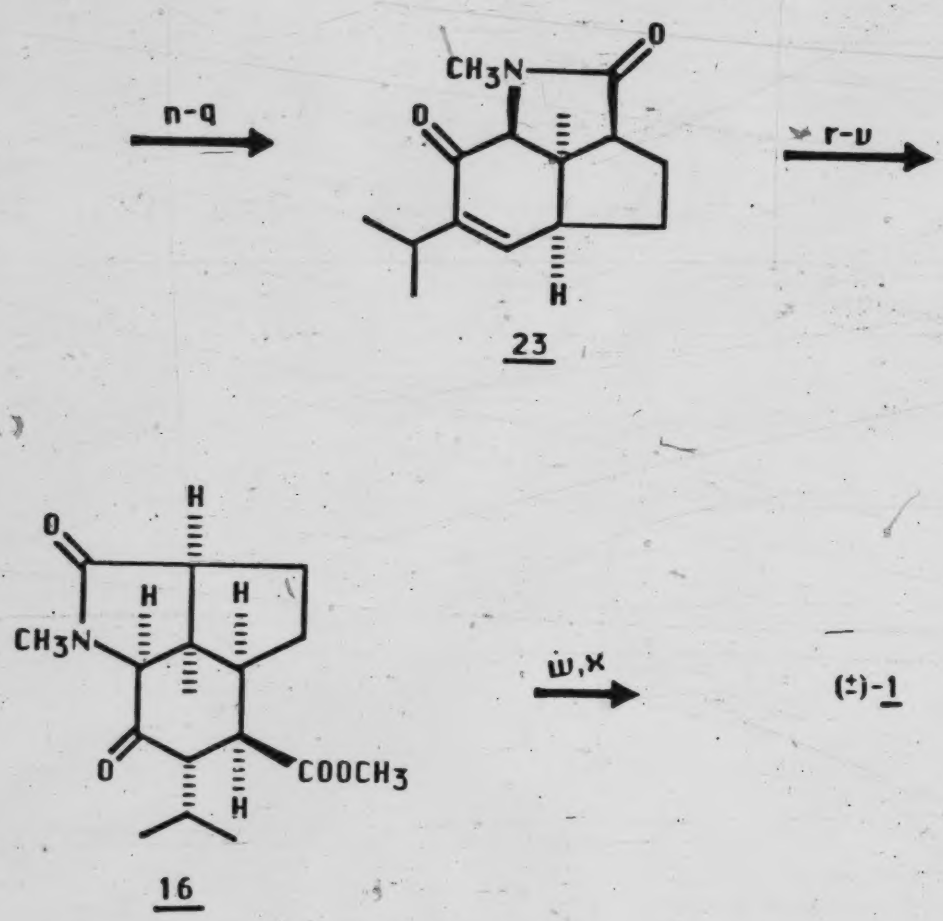
16

(±) -1

a: $Ac_2O$, p-TsOH, reflux; b: $O_3$,MeOH, DMS, -75°C; c: hydrolysis; d: $(Ph)_3P^+$-$CH(CH_3)$-$OCH_3Cl^-$, $CH_3$-SO-$CH_2^-$ $Na^+$, DMSO, glyme, -40°C; e: $(COOH)_2$,$H_2O$; f: HO-$CH_2CH_2$-OH, $(COOH)_2$,reflux; g: Li,$NH_3$, t-BuOH, THF, -35°C; h: $(COOH)_2$,$H_2O$; i: 1:1 EtOH, 0.4N HCl, reflux; j: t-BuOK, t-BuOH, reflux; k: Seperation l:$CH_2N_2$; m:$Ac_2O$, 10- Camphorsulfonic acid; n: $O_3$,EtOAc, $H_2O$, 0°C; o: N,N'- Carbonyl-di-imidazole, 80°C, heat, 5 minutes p: 1:1 40%aq. $CH_3NH_2$ - glyme; q: Pyridinum bromide perbromide; r: NaH, glyme, reflux; s: $(COOH)_2$; t: HCOOMe, NaOMe, benzene; u: n-BuSH, 10- Camphorsulfonic acid; v: $Me_2CuLi$, -40°C, ether; w: NaH, glyme, reflux; x: $NaBH_4$,EtOH; y: Triethyloxoniumfluoroborate; z:$NaBH_4$, glyme.

SCHEME III





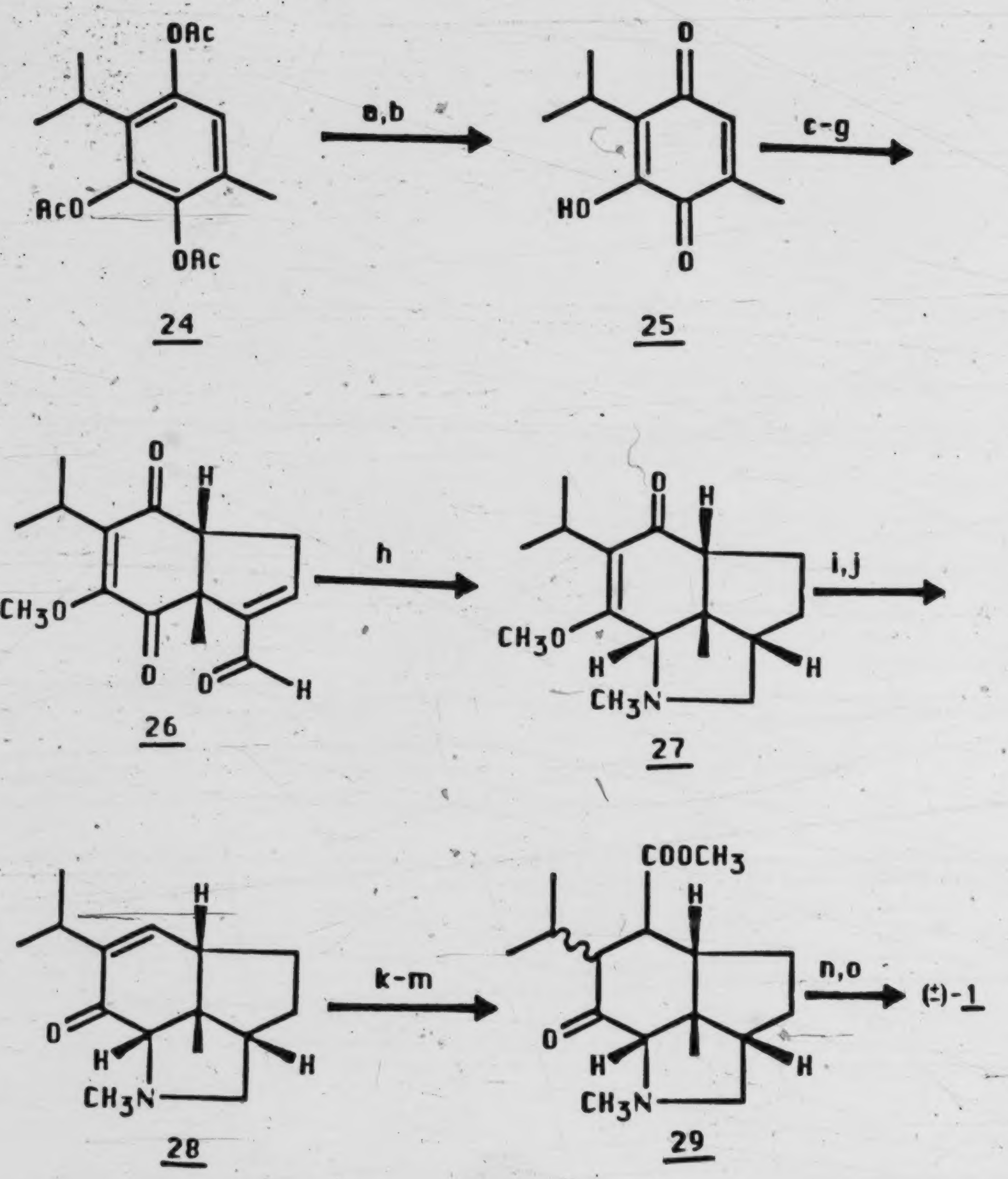
a: $NaBH_4$; b: Pyridine, TsCl; c: NaCN, DMSO, d: $H_2$,5% Pd-$SrCO_3$ ,MeOH; e: Recrystallization; f: $Br_2$ (1 eq); g: LiBr-$Li_2CO_3$,DMF; h: HO-$CH_2$-$CH_2$-OH, p-TsOH, benzene; i: NaOH; j: p-TsOH; k: 25%$H_2SO_4$, HO-$CH_2$-$CH_2$-OH; l: 30% aq. $CH_3NH_2$,$CH_3NH_2$.HCl,180-190°C ; m: $(CH_3)_2CHMgBr$,ether, -70- -60°C; n: $KHSO_4$; o: $I_2$ ,$CH_3COOAg$,ACOH; p: KOH,MeOH; q: $CrO_3$, pyridine; r: $Et_2AlCN$ ; s: $H_2SO_4$,ACOH; t: $CH_2N_2$; u: $NaBH_4$; v: KOH; w: Triethyloxoniumfluoroborate; x: $NaBH_4$, glyme.

lactam **21** which upon treatment with isopropyl magnesium bromide afforded the alcohol **22**. Subsequent functional group manipulations gave compound **23**. Nagata's hydrocyanation method was used to convert compound **23** to a nitrile which was further elaborated to (±)-oxodendrobine **(16)**. The compound **16** was converted to dendrobine (**1**) by the same procedure used by Yamada *et al*.

In Kende's synthesis of dendrobine,[20] the known triacetate **24** was used as the starting material. Conversion of **24** to the quinone **25** (Scheme IV) was effected by saponification followed by ferric chloride oxidation. Diels-Alder reaction between **25** and butadiene gave a 1:1 adduct which underwent a ring cleavage reaction and aldol condensation to give the hydrindanone derivative **26**. Reductive amination of **26** gave the amine **27**. Sequential treatment of **27** with lithium aluminum hydride and 2 N cold sulphuric acid provided the enone **28**. The enone **28** was subsequently elaborated to the keto ester **29**. Sodium borohydride reduction of **29** in isopropyl alcohol gave (±)-dendrobine (**1**).

Roush[21] utilized an intramolecular Diels-Alder reaction to build the hydrindane system possessed by dendrobine (**1**). The triene **30** was prepared from the lithio salt of methyl 4-(diethylphosphono)crotonate in seven steps. Diels-Alder reaction of the trimethylsilyl

## SCHEME IV



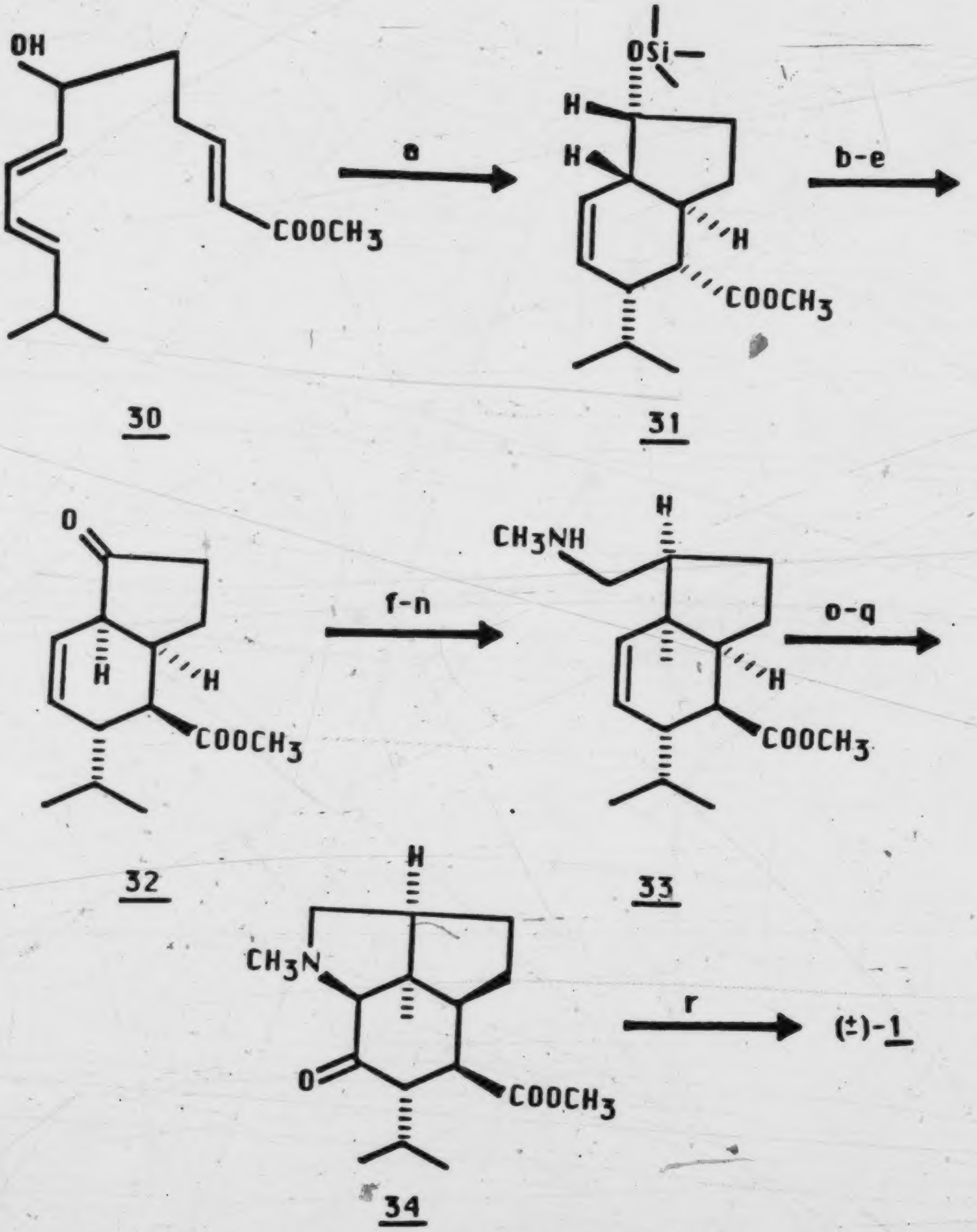
a: MeOH, $K_2CO_3$; b: $FeCl_3$; c: Isoprene, EtOH, 110°C; d: NaH, $CH_3I$; e: $OSO_4$, $Ba(ClO_3)_2$, aq. Dioxane; f: $HIO_4$, THF; g:Pyrrolidineacetate, benzene; h: $CH_3NH_2.HCl$, $NaCN.BH_3$, ph-5, MeOH, 20°C; i: LAH, ether, 25°C; 2N $H_2SO_4$; k: Lithiumdivinylcuprate,ether,-20°C; l: $RuO_4$,AcOH, 25°C; m: $CH_3NH_2$,ether,20°C; n: 0.3 M NaOMe, MeOH; o: $NaBH_4$, i-propanol.

derivative of **30** in toluene afforded compound **31** as the major product. Removal of the silyl group followed by a series of functional group manipulations gave the keto ester **32**. The angular methyl group was introduced at this stage and the resulting compound was converted to the amino ester **33** in six steps. The amino ester **33** was protected with 2,2,2-trichloroethylchloroformate and the resulting compound was elaborated to the keto ester **34**. The keto ester **34** was converted to (±)-dendrobine (**1**) using the same procedure by Kende.[20]

About a decade ago, a method for the regioselective construction of the hydrindanone system was developed in our laboratory.[21] It involves 2 + 2 photocycloaddition and ring expansion reactions as the key steps. For example, isophorone when irradiated with vinyl acetate in benzene afforded a mixture of photoadducts. The adducts were subsequently transformed to the ketone **35** (Scheme VI). Ring expansion of **35** with ethyl diazoacetate in the presence of boron trifluoride etherate gave the regioisomer **36** predominantly. This ring expansion process was regioselective and occurred by the preferential migration of the less substituted α carbon.

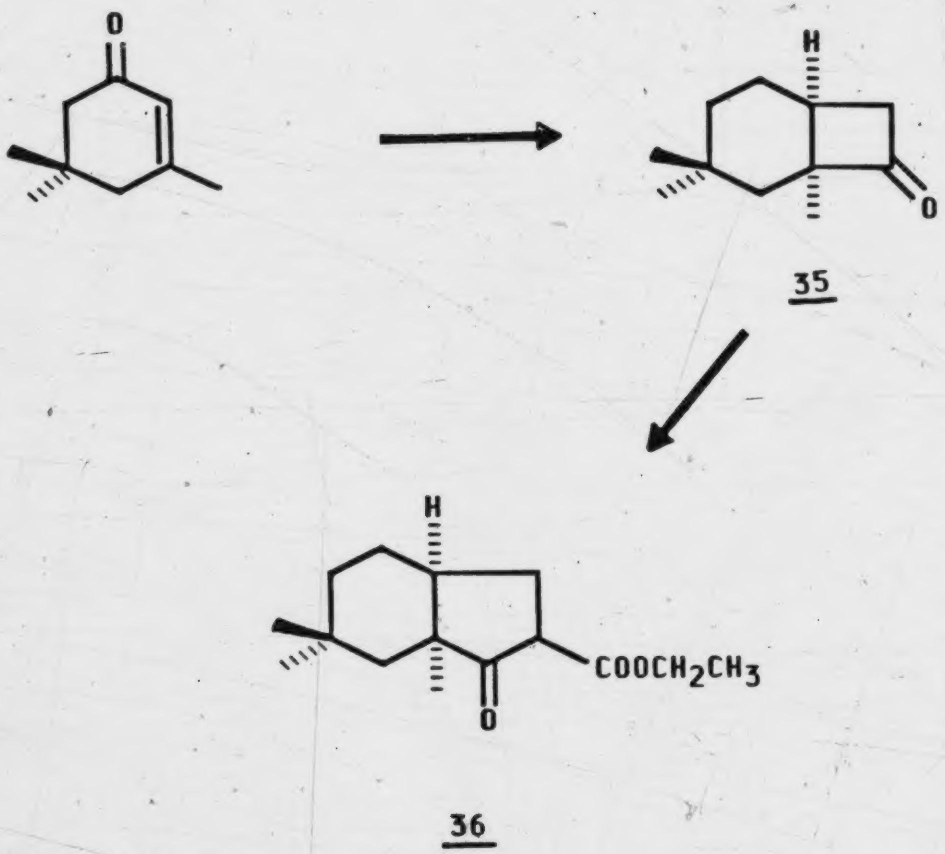
Using piperitone **37** as a starting material, the application of the above method to the construction of the hydrindanone system present in dendrobine (**1**) can easily

## SCHEME V

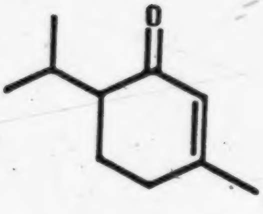


a: BSA, toulene; b: 1N HCl; c: NaOMe, MeOH; d: TFAA, DMSO; e: DME, t-BuOK, t-BuOH, $CH_3I$; f: t-BuOK, t-BuOH, Tosylmethylisocyanide; g: $H_2O_2$, NaOH, EtOH; h: NBS, THF, $H_2O$; i: Zn, AcOH, reflux; j: Oxalyl chloride; k: $Li(t\text{-}BuO\text{-})_3AlH$, THF, 0°C; l: $CH_3SO_2Cl$, $NEt_3$, $CH_2Cl_2$, 0°C; m: DMSO, ex $CH_3NH_2$, 85°C, 18h; n: $CCl_3CH_2OCOCl$, pyridine, $CH_2Cl_2$; o: MCPBA, 4',4,-Thiobis (6-tert-butyl-3-methylphenol), toulene; p: 1:1 acetone, 2N HCl, ex Jones; q: $NaBH_4$, i-propanol.

## SCHEME VI



be conceived. Irradiation of piperitone with a ketone equivalent, such as vinyl acetate, would give a bicyclic system of the type **38**. Compound **38**, after the necessary functional group modifications, could be transformed to **40** via the enone **39**. The cyclobutanone portion of **40** could then be ring expanded and decarboxylated to the diketone **41**, an important precursor towards the total synthesis of dendrobine (1). Details of the efforts made towards the synthesis of a precursor of the type **41** are outlined in the first chapter of this thesis.



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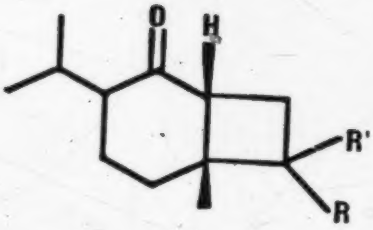

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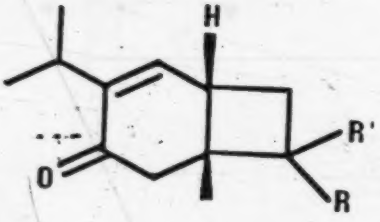

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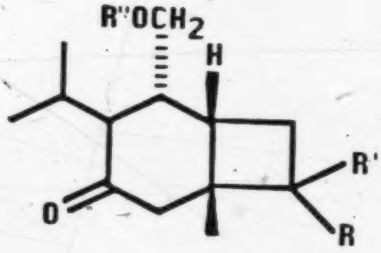

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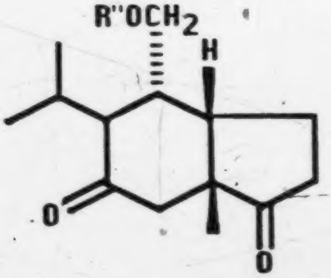

41

## RESULTS & DISCUSSION

As discussed previously, 6-isopropyl-3-methylcyclohex-2-en-1-one (piperitone) (**37**) was conceived as the ring B equivalent of dendrobine (**1**). It not only possesses the correct substitution pattern needed but also lends itself as a good starting material for a chiral synthesis of dendrobine (**1**).

Both the levorotary[22] and dextrorotary[23] forms of piperitone are available in nature. Furthermore the racemic form* which was used for the present work, can easily be prepared from 2-isopropyl-5-methylanisole by Birch reduction[24] using lithium in liquid ammonia followed by hydrolysis with aqueous hydrochloric acid.

From the retrosynthetic analysis, the immediate task was to prepare the bicyclo[4.2.0]octane derivative **38** from piperitone (**37**). This can be done by a photochemical addition of a ketene equivalent, in a head-to-tail fashion, to the carbon-carbon double bond of the starting enone **37**. Several ketene equivalents are available. allene[26] is known to give the head-to-head photoadduct while vinyl esters[27] and 1,1-dialkoxyethenes[28-30] are known to undergo head-to-tail additions. Both 1,1-diethoxyethene and vinyl acetate were employed in this work. The latter compound, being cheap and commercially available, was used for most of the preparations undertaken.

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* For other methods of preparation, see Ref. 25.

Irradiation of a benzene[28] solution of piperitone (**37**) and an excess of vinyl acetate with a 450 W Hanovia medium pressure mercury lamp, using a Pyrex filter, afforded a mixture of photoadducts. The $^1$Hmr spectrum of the mixture displayed four methyl singlets around $\delta$1.20. It could be inferred that the mixture was made up of at least four compounds. These compounds could be both stereoisomers as well as regioisomers.[26,28] However, in photocycloadditions of enones to vinyl acetate, the head-to-tail adducts are usually formed preferentially. It is therefore likely that the mixture would contain mainly the adducts with the desired regiochemistry and the difference might be due to the stereochemistry at the three newly created asymmetric centers.

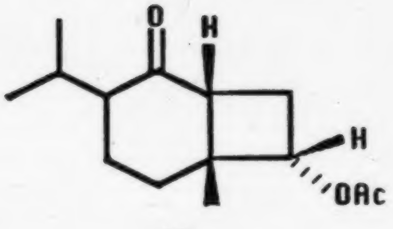
The trans ring junction should be easily equilibrated to the thermodynamically more stable cis form[28] in the mixture of adducts by base treatment. This would also result in a less complex mixture, which should be easier to purify. The mixture, after treatment with 1,5-

diazabicyclo[4.2.0]undec-5-ene in benzene at reflux, gave two products in a ratio of 1:5 in 65% yield.

The minor product showed ir absorption bands at 1739 and 1705 $cm^{-1}$ indicative of the presence of an ester and ketone respectively. That the former was an acetate functionality was confirmed by its $^{1}$Hmr spectrum which showed a methyl singlet at $\delta$2.08 as well as a broad doublet (J = 10 Hz) at 4.86 due to the methine proton adjacent to the acetate group. A singlet at $\delta$1.22 was assigned to the angular methyl group. Two doublets at $\delta$0.96 and 0.86 (J = 8 Hz each) were assigned to the isopropyl methyl groups. The mass spectrum showed a peak at m/e 196.1454 ($M^{+}$-42) accounting for the chemical formula $C_{12}H_{20}O_{2}$.

The major product showed ir absorption bands at 1740 and 1720 $cm^{-1}$ for the ester and the ketone respectively. In the $^{1}$Hmr spectrum, a singlet at $\delta$2.02 was due to an acetate methyl and a triplet (J = 9 Hz) at $\delta$4.74 was due to the methine proton adjacent to the acetate group. The mass spectrum displayed a molecular ion peak at m/e 238.1568 for the chemical formula $C_{14}H_{22}O_{3}$.

A closer analysis of the spectral data suggested that the two products have the structures **42** and **43**, and are epimeric only at C-7. The broad doublet and a triplet at $\delta$4.86 and 4.74 respectively for the methine protons



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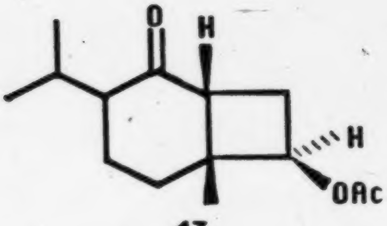

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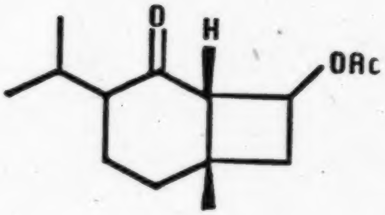

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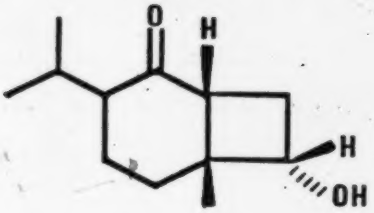

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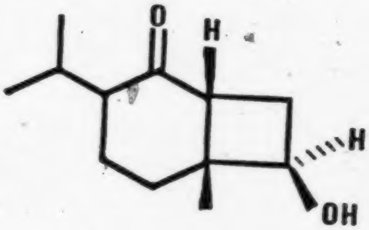


46

adjacent to the acetate group in **42** and **43** indicated that there were only two protons adjacent to each of them. A different splitting pattern would have been observed if it had been the corresponding methine protons of the regioisomeric ketones **44**, in which case there would have been three adjacent protons.

The ring junction stereochemistry of both compounds could be easily assigned as cis, since it has been well established that the trans ring junctions of bicylco[4.2.0]octan-2-one systems can easily be epimerized to the thermodynamically more stable cis form.[28] The stereochemistry at the center bearing the isopropyl group was not determined at this stage. Further confirmation of the foregoing structural assignment was obtained from experiments performed on the respective alcohols.

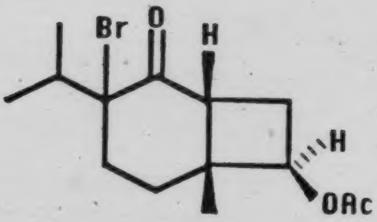
Keto acetate **42** was treated with potassium carbonate in aqueous methanol[31] at reflux temperature to give a pure alcohol **45** in quantitative yield. The ir spectrum showed bands at 3389 and 1700 $cm^{-1}$ due to the hydroxy and the saturated ketone respectively. A broad doublet ($J = 8.5$ Hz) at $\delta$4.12 in the $^1$Hmr spectrum was due to the methine proton adjacent to the alcohol. The mass spectrum showed a molecular ion peak at m/e 194.1464 for the chemical formula $C_{12}H_{20}O_2$. The keto acetate **43** was similarly hydrolyzed to alcohol **46** in quantitative yield. The ir spectrum showed an absorption band at 3380 $cm^{-1}$ due to the hydroxyl group and another at 1701 $cm^{-1}$ due to a saturated ketone. The methine proton adjacent to the hydroxyl group appeared at $\delta$4.02 as a triplet (J = 8 Hz) in the $^1$Hmr spectrum. The mass spectrum showed a molecular ion peak at m/e 196.1465 for the chemical formula $C_{12}H_{20}O_2$.

A two-dimension NOE experiment performed on the alcohol **45** indicated that the methine proton on C-7 at $\delta$4.12 had NOE's with protons at C-1 and C-8 as well as with those on the angular methyl group. Since NOE effects are observed only when groups are oriented in the same direction in space, this establishes a cis relationship between the methine proton on C-7, the angular methyl group, and the proton on C-1.

Normal NOE experiment was also done with the alcohol **45**. A 25% enhancement was observed on the signal at $\delta$4.12 when the signal for the angular methyl group was irradiated. On the other hand no NOE was observed upon irradiation of the same methyl signal in the alcohol **46**. This confirmed that the stereochemistry of the alcohols at C-7 was indeed as shown in **45** and **46**. Since no epimerization could have occurred during the hydrolysis of their corresponding acetates **42** and **43**, the NOE experiments also established the stereochemistry of the acetates at C-7 as shown in **42** and **43**.

Having obtained the bicyclic system of the type **38**, in the form of acetates and alcohols above, it was decided to explore the possibilities of introducing a double bond in the six-membered ring which would allow for further elaboration to an enone of the type **39**. The initial idea was to introduce the double bond in the acetates **42** and **43** or in the alcohols **45** or **46**. Various methods are available for such an operation.[32-40]

Pyridinium bromide perbromide[32] is known to brominate $\alpha$ positions of ketones and the resulting bromides could be dehydrobrominated[33] to give the corresponding enones. Treatment of acetate **43** with pyridinium bromide perbromide in glacial acetic acid overnight, gave the bromo acetate **47**, in 25% yield. The ir spectrum showed bands at 1746 and 1725 $cm^{-1}$ due to acetate and ketone respectively. The $^1$Hmr spectrum displayed a doublet of triplets (J = 8, J' = 1 Hz) at $\delta$4.88 which was assigned to the methine proton adjacent to the acetate group. A doublet of doublets of doublets (J = 10, J' = 5, J" = 1 Hz) at $\delta$2.96 was assigned to the angular methine proton. Singlets at $\delta$2.08 and 1.30 were assigned to the angular and acetate methyl groups respectively. Two doublets (J = 8 Hz each) at $\delta$1.18 and 1.02 were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 316.0625 due to the chemical formula $C_{14}H_{21}BrO_3$. Other products



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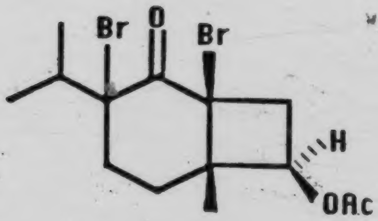

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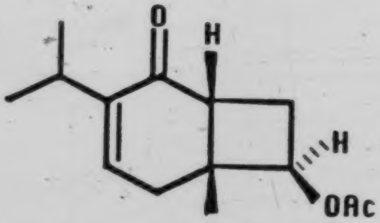

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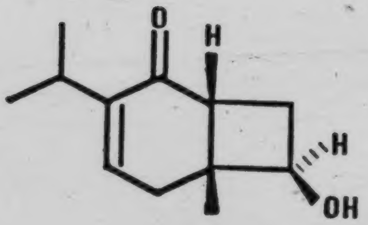


50

isolated were the dibromide **48** (26% yield) and the starting acetate **43**.

When the bromoacetate **47** was refluxed in pyridine the enone acetate **49** was obtained in 94% yield. The ir spectrum displayed bands at 1744 and 1670 cm$^{-1}$ for the acetate and enone respectively. The $^1$Hmr spectrum showed two triplets at $\delta$6.64 (J = 4 Hz) and 4.94 (J = 8 Hz) due to the enone proton and the methine proton adjacent to the acetate group respectively. The $^{13}$Cmr spectrum displayed signals at $\delta$199.9 and 170.7 which were assigned to the enone and acetate carbonyl carbon atoms respectively. Two other signals at $\delta$144.8 and 139.8 were assigned to the $\beta$ and $\alpha$ carbon atoms of the enone moiety. The mass spectrum showed a molecular ion peak at m/e 236.1368 indicating the chemical formula $C_{14}H_{20}O_3$.

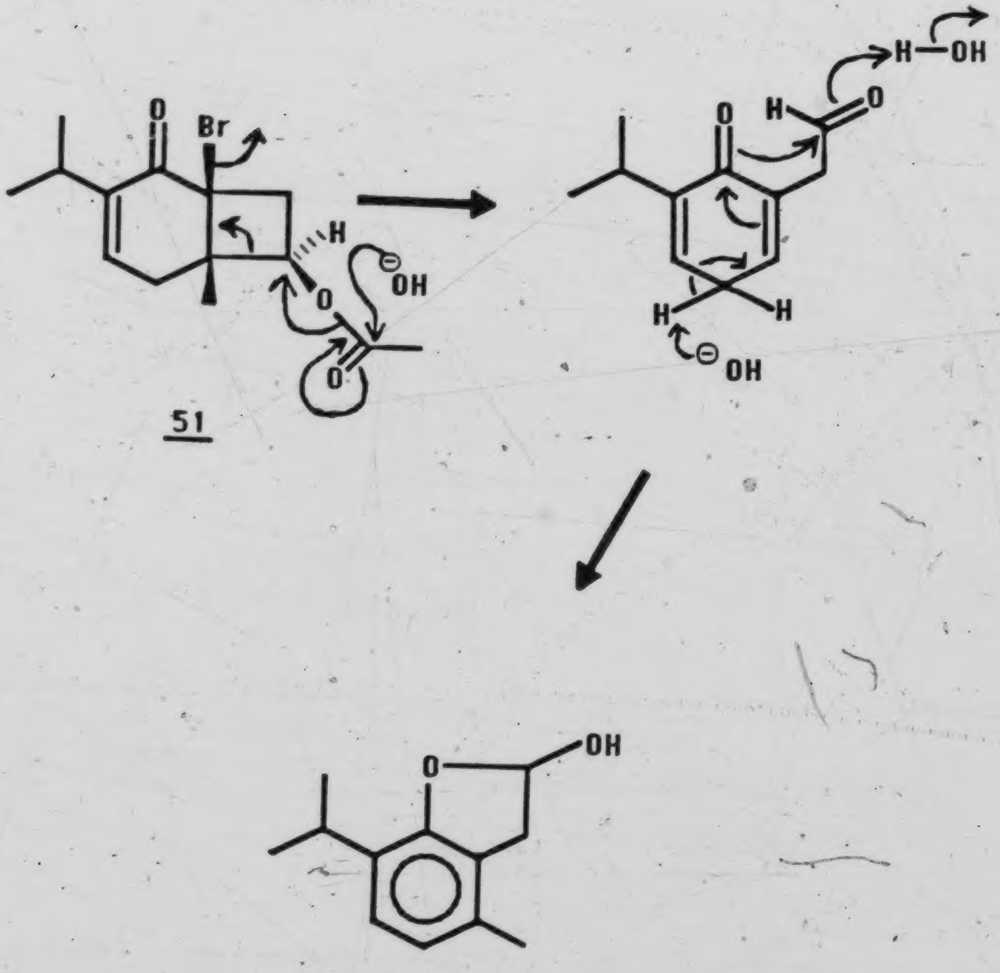
Hydrolysis of the enone **49** with potassium carbonate in refluxing aqueous methanol gave the enone alcohol **50** in quantitative yield. The ir spectrum showed a hydroxyl band at 3440 cm$^{-1}$. The other bands at 1660 and 1640 cm$^{-1}$ were attributed to the enone ketone and the double bond respectively. The $^1$Hmr spectrum exhibited a doublet of doublets of doublets (J = 6, J' = 3, J" = 1 Hz) at $\delta$6.56 which was attributed to the enone proton. A broad triplet (J = 7 Hz) at $\delta$4.26 was assigned to the methine proton adjacent to the hydroxyl group. The septet (J = 7 Hz) at

$\delta$2.96 was attributed to the isopropyl methine proton. The angular methyl group appeared as a singlet at $\delta$1.28 while the isopropyl methyls appeared as doublets (J = 7 Hz each) at $\delta$1.04 and 1.00. The mass spectrum showed a molecular ion peak at m/e 194.1309 for $C_{12}H_{18}O_2$.

The dibromide **48** in pyridine at reflux temperature gave the monobromide **51**, which upon exposure to potassium carbonate in refluxing aqueous methanol underwent a Grob fragmentation,[41] as indicated, and aromatization to the lactol **52** (Scheme VII) exclusively. The ir spectrum of **52** showed bands at 3444 $cm^{-1}$ due to the hydroxy group. The $^1$Hmr spectrum exhibited two doublets (J = 8 Hz each) at $\delta$7.04 and 6.74 for the aromatic protons. Two doublet of doublets (J = 8, J' = 2 Hz each) at $\delta$6.13 and 3.32 were attributed to the hemiacetal methine and a benzylic methylene proton respectively. Another doublet of doublets at $\delta$2.96 was attributed to the other benzylic methylene proton. The singlet at $\delta$2.22 was due to the aromatic methyl group. The septet (J = 8 Hz) at $\delta$3.12 and a doublet (J = 8 Hz) at $\delta$1.24 were assigned to the isopropyl methine and methyl groups respectively. The mass spectrum showed a molecular ion peak at m/e 192.1148 indicative of the chemical formula $C_{12}H_{16}O_2$.

The keto acetate **42** was similarly treated with pyridinium bromide perbromide in glacial acetic acid to

## SCHEME VII



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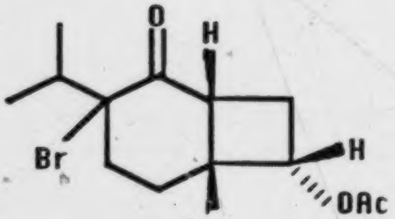
52

give the bromo acetate **53** together with the corresponding dibromide and starting material. The bromo acetate **53** upon reflux in pyridine gave the enone acetate **54** in 90% yield. The ir spectrum showed bands at 1743 and 1665 cm$^{-1}$ due to acetate and enone respectively. The $^1$Hmr spectrum displayed a broad doublet (J = 4 Hz) at δ6.58 which was assigned to the enone proton. Doublets (J = 8 Hz each) at δ5.08, 1.04 and 1.00 were assigned to the methine proton adjacent to the acetate group and the isopropyl methyl groups respectively. Singlets at δ2.08 and 1.24 were attributed to the acetate and angular methyl groups. The mass spectrum exhibited a molecular ion peak at m/e 236.1364 accounting for the chemical formula $C_{14}H_{20}O_3$. Treatment of the enone acetate **54** with potassium carbonate in refluxing aqueous methanol gave the enone alcohol **55** in quantitative yield. The dibromide, upon reflux in pyridine followed by hydrolysis with potassium carbonate in refluxing aqueous methanol, underwent a fragmentation to the lactol **52**.

The bromination reaction was also investigated with the alcohols **45** and **46**. Treatment of alcohol **45** with pyridinium bromide perbromide in glacial acetic acid gave the bromoacetate **53** in 38% yield, together with the dibrominated acetate and acetate **42**. Apparently, the mixture of acetic acid and the hydrogen bromide generated during the reaction served as an acetylating agent for the hydroxyl function. Dehydrobromination of **53** was readily achieved in refluxing pyridine to the enone **54**, which was hydrolyzed to the alcohol **55**, with potassium carbonate in refluxing aqueous methanol. The alcohol **46** was also converted to the alcohol **50** by bromination with pyridinium bromide perbromide, dehydrobromination of the resulting bromide in refluxing pyridine followed by hydrolysis with potassium carbonate in aqueous methanol at reflux. The dibromides obtained from the bromination reactions, when exposed to dehydrobromination in refluxing pyridine followed by hydrolysis gave the lactol **52**.

With the enone alcohols **50** and **55** in hand, the stage was set for the oxidation[42-45] of the hydroxyl group to the ketone. The method used in this connection was the Goodmann's modification[42] of the Moffat[43] oxidation. Treatment of the enone alcohol **50** with acetic anhydride in dimethylsulfoxide at 7°C afforded a 70% yield of the enone ketone **56**. The ir spectrum displayed bands at 1782 and 1670 $\text{cm}^{-1}$ for the four-membered ring ketone and enone respectively. In the $^1$Hmr spectrum, a doublet of doublet of doublets ($J = 6$, $J' = 2.5$, $J'' = 1$ Hz) at $\delta$6.50 was assigned to the enone proton. Two doublets of doublets at $\delta$3.60 ($J = 17.5$, $J' = 10$ Hz) and $\delta$2.84 ($J = 17.5$, $J' = 5$ Hz) were assigned to the methylene protons of the



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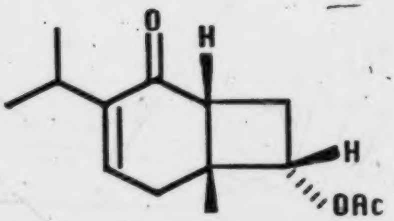

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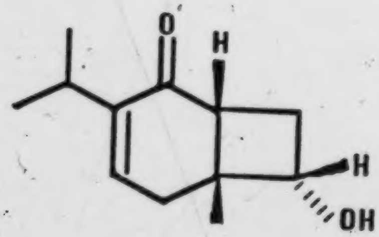

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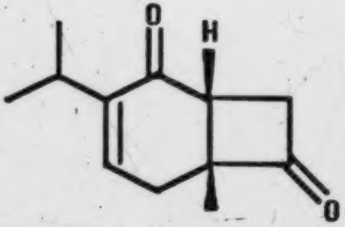


56

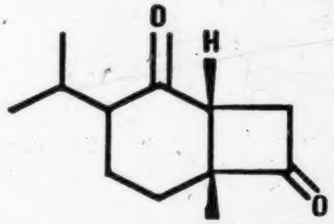
cyclobutanone moiety. Another doublet of doublets (J = 10, J' = 5 Hz) at δ3.00 was assigned to the angular methine proton. The angular and isopropyl methyl groups appeared as a singlet at δ1.33 and a pair of doublets at δ1.08 and 0.98 respectively.

Even though the enone ketone **56** was the target molecule in the series of experiments described, the bromination step proceeded with very low yields. The best yield of monobromide was 25% when the acetates were used and 38% in the case of the alcohols. Selective monobromination appeared to be difficult, since dibromination also occurred to a great extent. It was therefore deemed necessary to explore other alternatives to introduce the double bond.

This time around, we sought to convert the alcohols **45** and **46** to the corresponding diketones before introducing the double bond in the six-membered ring. The Swern's modification[44] of the Moffat oxidation was used instead of the Goodmann's, since it involved the use of a lesser amount of dimethylsulfoxide, removal of which was found to be rather difficult on a larger scale.

Thus the alcohol **45** was added to a mixture of oxalyl chloride and dimethylsulfoxide in dichloromethane at -60°C and triethylamine was added to give a single product as a solid, m.p. 60-61°C, in 33% yeild. The alcohol **46** was also oxidized under similar conditions, as described above, to give the same product. The compound showed bands in the ir spectrum at 1779 and 1705 $cm^{-1}$ indicative of four- and six-membered ring ketones respectively. The $^{1}$Hmr spectrum showed two doublets of doublets at $\delta$3.64 (J = 18, J' = 11.5 Hz) and $\delta$2.98 (J = 18, J' = 5.5 Hz) respectively for the methylene protons $\alpha$ to the four-membered ring ketone. Another doublet of doublets (J = 11.5, J' = 5.5 Hz) at $\delta$3.14 was assigned to the ring junction methine proton. Even though the mass spectrum showed a molecular ion peak at m/e 194.1267 for the expected diketone, a more intense peak at m/e 193 ($M^{+}$-1) was also exhibited. Furthermore, there were less intense peaks at m/e 228.0924 and 230.0897. The elemental analysis based on the diketone **57** also deviated by a surprisingly large amount (C ~ 12%, H ~ 2%). We at this stage suspected that the molecule might have an element, other than carbon and hydrogen. Various methods of introducing the double bond were examined using this compound.

Upon treatment of the diketone with pyridinium bromide perbromide in glacial acetic acid, a mixture of products were obtained. When the mixture was refluxed in pyridine, it was completely converted to the lactone **58**, m.p. 77-79°C. The ir spectrum showed a band at 1807 $cm^{-1}$



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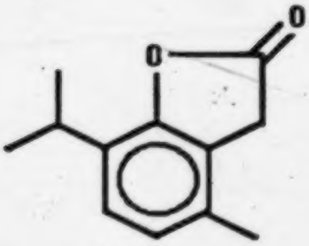

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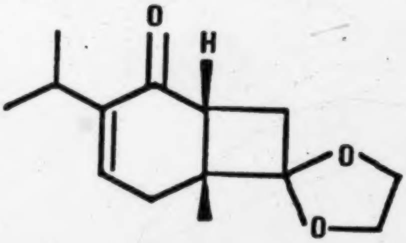

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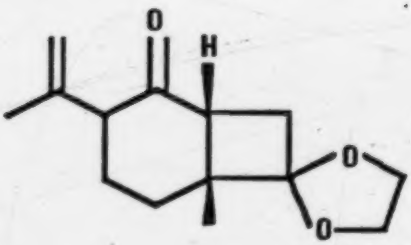

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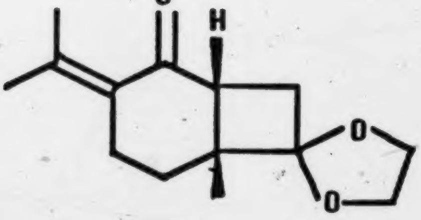

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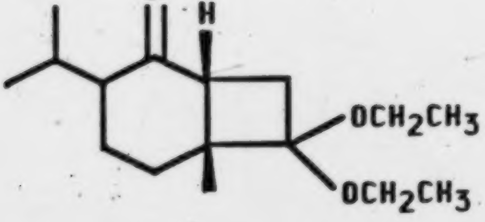

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due to the enol $\gamma$-lactone, and others at 1640, 1625, and 1600 $cm^{-1}$ for the aromatic ring. The $^{1}$Hmr spectrum showed an AB pattern of two doublets (J = 8 Hz each) at $\delta$7.14 and 6.92 for the aromatic protons. Two singlets at $\delta$3.62 and 2.3 were assigned to the benzylic methylene protons and the aromatic methyl group respectively. A doublet at $\delta$1.26 was assigned to the isopropyl methyl groups. The mass spectrum exhibited a molecular ion peak at m/e 190.0991 indicative of the chemical formula $C_{12}H_{14}O_2$. Formation of dibrominated compounds, which induced the rapid aromatization of the compound was attributed to the production of 58. It was therefore decided to protect the four-membered ring ketone and to try other methods of introducing the double bond in the resultant monoketone.

Attempted protection[46-48] of the four-membered ring ketone, under the usual conditions, with ethylene glycol[47] gave a mixture of mono- and diketalized products. Since no selectivity was observed under the above conditions, attention was turned to the use of 2-ethyl-2-methyl-1,3-dioxolane[48] as a reagent.

Exposure of the diketone to ketalization conditions using 2-ethyl-2-methyl-1,3-dioxolane in the presence of a catalytic amount of p-toluenesulfonic acid gave the monoketal in 74% yield. The ir spectrum showed a band at 1700 $cm^{-1}$ due to a saturated ketone. The $^{1}$Hmr spectrum exhibited a multiplet at $\delta 3.90$ attributed to the ethylene ketal methylene protons. A singlet at $\delta 1.24$ was assigned to the angular methyl group. The mass spectrum showed a peak at m/e 238.1569 for the chemical formula $C_{14}H_{22}O_3$.

When the monoketal was treated with pyridinium bromide perbromide in pyridine, while only starting material was recovered at room temperature, a mixture of complex products were obtained upon reflux. Treatment of the monoketal in carbon tetrachloride with molecular bromine[32] did not give any detectable products, only starting material was recovered. The use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[35] led to decomposition products. On exposure of the monoketal to lithium diisopropylamide, generated in situ from diisopropylamine and n-butyllithium, followed by treatment with phenylselenenyl bromide[33] and oxidation with aqueous hydrogen peroxide, the starting monoketone was recovered intact.

Sulfuryl chloride,[36] which is known to be a selective chlorinating agent, was also tried. However, when the monoketone in carbon tetrachloride was treated with sulfuryl chloride, the starting material was recovered intact even after four days.

Saturated ketones are known to form silyl enol ethers[37] which upon treatment with palladium acetate[38] afford enones in good yields. This method was examined with the monoketone.

The monoketone in dimethylformamide was added to a mixture of triethylamine and chlorotrimethylsilane and heated to 130-135°C (oil bath temperature). The crude product showed absorption bands in the ir spectrum at 1705 and 1671 $cm^{-1}$ due to saturated ketone and enone respectively. The $^1$Hmr spectrum displayed a triplet (J = 8 Hz) at $\delta$ 6.6 characteristic of the $\beta$-proton of an enone. Two broad doublets at $\delta$ 5.82 and 4.82 were attributed to vinylic protons. There were four methyl singlets at $\delta$ 2.16, 2.02, 1.86, and 1.24 and a doublet at $\delta$ 1.04. The mass spectrum showed a molecular ion peak at m/e 236.1604 indicative of the chemical formula $C_{14}H_{20}O_3$. The spectral data suggested that a mixture consisting of compounds **59**, **60**, and **61** was formed.

Double bonds are known to move into conjugation[49] with carbonyl groups very rapidly. It is also known that in cyclohexane rings, endo double bonds are thermodynamically more favored over exo.[50] Compounds **60** and **61** should therefore be expected to be converted to the enone **59** under equilibrating conditions. It was however, recognized that under acidic conditions protonation of the double bond would lead to the creation of a positive charge $\alpha$ to a carbonyl, which would be a highly unstable species. In order to circumvert this situation, it was decided to convert the ketone to a ketal. By having a ketal, the positive charge so created upon protonation of the double bond would be stable enough to allow for an efficient production of the enone **59** after deketalization. The mixture **59-61** was therefore dissolved in benzene and refluxed in the presence of _p_-toluenesulfonic acid and ethylene glycol with the azeotropic removal of the benzene-water admixture. The crude product showed no absorption in the ir spectrum between 1800 and 1650 $cm^{-1}$. It was then treated with aqueous oxalic acid in refluxing acetone.

The major product **59** displayed a band in the ir spectrum at 1665 $cm^{-1}$ accounting for an enone. The $^1$Hmr spectrum showed a triplet (J = 6 Hz) at $\delta$6.60 for the enone proton. A multiplet at 3.92 was assigned to the ethylene ketal protons, which also confirmed that the cyclobutanone portion was still protected. A methyl singlet at $\delta$1.24 and a doublet at $\delta$1.04 for the remaining methyl groups confirmed the presence of a single compound. The mass spectrum showed a molecular ion peak at m/e 236.1408 for the chemical formula $C_{14}H_{20}O_3$.

The above results led us to examine the same silylation reaction on the diketone, to see if a similar behaviour would be observed and maybe shed some light on what went on during the reaction with the monoketone.

Thus the diketone was treated with a mixture of triethylamine and chlorotrimethylsilane in dimethylformamide at 130°C. An enone which showed identical characteristics as compound **56** was obtained. Still unsure of what was going on together with the rather unusual behaviour of the diketone, we decided to prepare the diketone **57** from a completely different route.

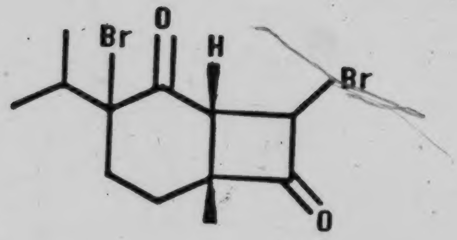
Apart from the fact that a correlation between the diketones could be undertaken, the method to be used could improve the yield and also reduce the number of steps involved in the preparation of the enone **56**.

Compared to vinyl esters, dialkoxyethanes are known to exert a better regiochemical control in photocycloaddition reactions.[28] 1,1,-Diethoxyethene was therefore used as the ketene equivalent in place of vinyl acetate. This compound was readily prepared in large quantities by dehydrobromination of the commercially available bromoacetaldehyde diethyl acetal according to literature procedure.[52]

Irradiation of a solution of piperitone (**37**) and 1,1-diethoxyethene in benzene under similar conditions as described for the vinyl acetate reaction afforded a mixture of photoadducts in 80% yield. The ir spectrum of the mixture showed absorption bands at 1721 and 1706 $cm^{-1}$ due to saturated ketones. The $^1$Hmr spectrum showed multiplets between $\delta$3.7-3.44 and also between $\delta$1.34-1.20 characteristic of the ethoxy groups. The mass spectrum exhibited a molecular ion peak at 268.2032 which corroborated well with the chemical formula $C_{16}H_{28}O_3$. The spectral data suggested that the desired compound **62** was indeed formed. An attempted hydrolysis of the ketal with aqueous hydrochloric acid[53] gave only a small amount of the desired diketone, presumably due to the decomposition of the product under the reaction conditions. This problem was averted by carrying out the reaction with aqueous oxalic acid[54] or _p_-toluenesulfonic acid in refluxing acetone in the presence of a trace amount of water. The 2:1 mixture of two inseparable diketones **57** thus obtained in 75% yield displayed absorption bands, in the ir spectrum, at 1783 and 1700 $cm^{-1}$ for the four- and six-membered ketones respectively. The $^1$Hmr spectrum showed a pair of doublets of doublets at $\delta$3.48 (J = 18, J' = 11.5 Hz) and $\delta$3.00 (J = 18, J' = 6 Hz) together with another doublet of doublets (J = 11.5, J' = 6 Hz) at $\delta$2.74 which were assigned to the $\alpha$ methylene protons of the four-membered ring ketone and the angular methine proton respectively. Another pair of doublets of doublets at $\delta$3.42 (J = 18, J' = 10.5 Hz) and $\delta$3.26 (J = 18, J' = 6 Hz) and a further doublet of doublets (J = 10.5 Hz, J' = 6 Hz) at 2.76 were assigned to similar protons in the minor isomer. Singlets at $\delta$1.40 and 1.30 were assigned to the angular methyl group in the minor and major isomers respectively. Surprisingly, the diketone **57** differed from the diketone obtained earlier by the Swern's oxidation of the alcohols **45** and **46**, in its behaviour on thin layer chromatographic plate and also its spectral characteristics. Initially, they were assumed to be diastereoisomers. In an attempt to correlate them, the mixture of diketones **57** was subjected to epimerization using sodium methoxide in refluxing methanol. Extensive decomposition of material was observed under the conditions employed, and no conclusion could be drawn. In a further attempt to correlate the diketones, the mixture **57** was subjected to the bromination reaction with pyridinium bromide perbromide. Treatment of the diketone **57** with pyridinium bromide perbromide in glacial acetic acid gave a mixture of products. The ir spectrum of the mixture showed bands at 1794 and 1774 cm$^{-1}$ due to four-membered ring ketones and another set at 1746 and 1719 due to six membered ring ketones. The $^1$Hmr spectrum showed doublets (J = 10 Hz each) at $\delta$5.58 and 3.48 which were assigned to the four-membered ring ketone and the angular methine protons respectively. Another pair of doublets (J = 6 Hz each) at δ4.80 and 3.38 were assigned to similar protons in another isomer. The spectral data suggested the product to be a mixture of dibromides **63**. When the mixture was refluxed in pyridine, it gave a compound which was the same as lactone **58**, obtained previously by bromination-dehydrobromination of the diketone derived from the vinyl acetate adduct. All that could be concluded from this was that, the three diketones had the same basic skeletal frame work. Fortunately, the diketone from the vinyl acetate route was crystalline and was submitted for X-ray analysis.

The X-ray results (Fig. 1) indicated that a chlorine atom was situated at C-3 (labelled C-6 in Fig. 1) of the diketone obtained via the Swern oxidation, and that compound was therefore **64**. Chemical ionization mass spectrum showed the molecular ion peak to be indeed 228 ($M^+-18$). The $^{13}$Cmr spectrum displayed exactly twelve lines, two of which appeared at δ211.8 and 203.4 due to the six- and four-membered ring ketone carbon atoms.

Two important questions arise from the knowledge of the structure of **64**. Firstly, at which stage was the chlorine incorporated and secondly what served as the source of chlorine. No source of chlorine had been employed along the series until the Swern oxidation



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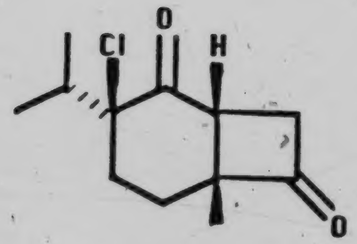

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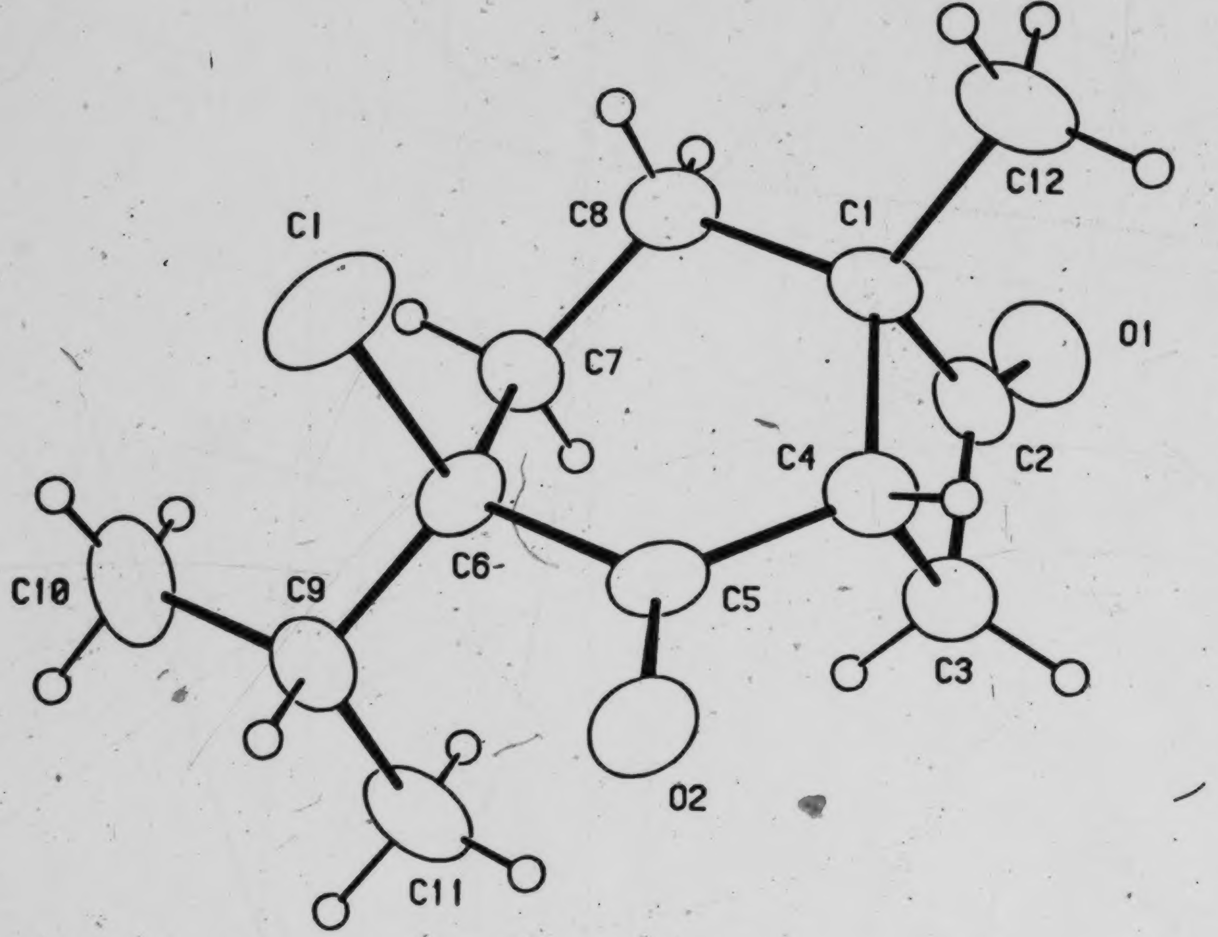


Fig. 1. X-ray Structure of Diketone 64.

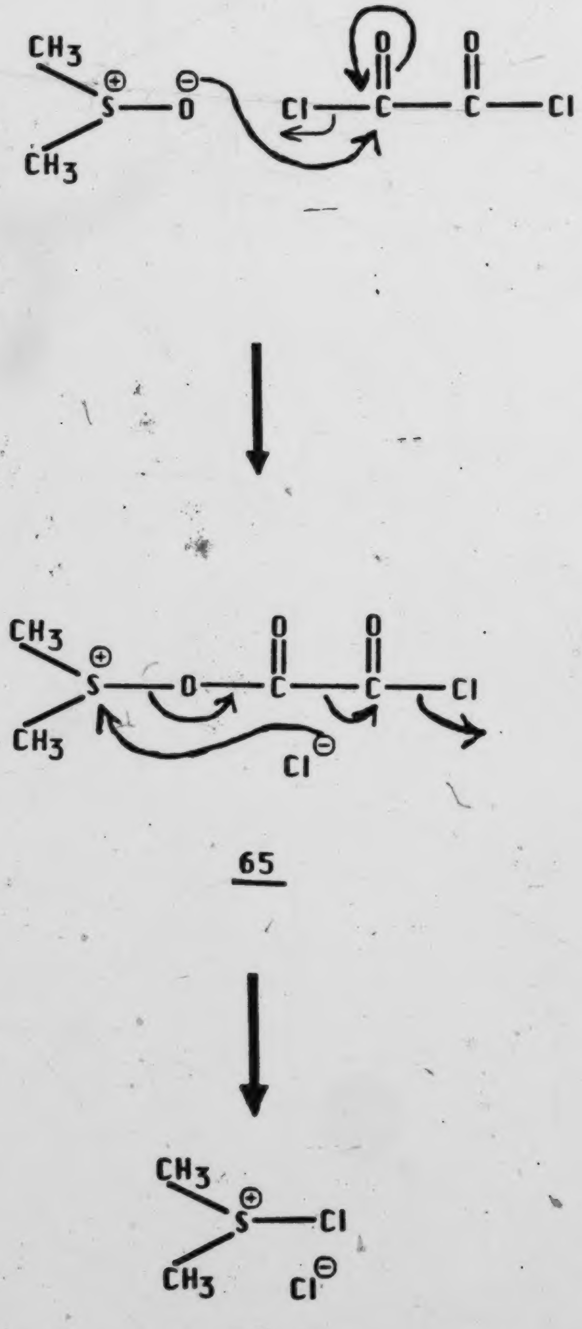
process, and the behaviour of the acetates and alcohols could be easily explained.

It was therefore decided to carry out the oxidation of the alcohols by some other means that would not involve any potential source of chlorine. The mixture of alcohols **45** and **46** were treated with acetic anhydride[41] in dimethylsulfoxide for 4 days at 5°C. The product obtained had the same spectral characteristics as the diketone **57**, obtained by the hydrolysis of the adduct **62**. This served to demonstrate that the chlorine atom was incorporated into the molecule during the Swern's oxidation. Furthermore, when the mixture of alcohols **45** and **46** was treated with a three-fold excess of oxalyl chloride and dimethyl sulfoxide at -60°C followed by triethylamine at 0°C, the yield of **64** was improved from 33% to 89%. A mixture of alcohols was also isolated. It showed absorption bands in the ir spectrum at 3420 and 1711 $cm^{-1}$ for hydroxyl and ketone respectively. The $^1$Hmr spectrum exhibited a broad doublet (J = 9 Hz) at $\delta$4.14 and a triplet (J = 8 Hz) at $\delta$4.04 for the methine proton adjacent to the hydroxyl group in the respective alcohols **45** and **46**. The mass spectrum exhibited a molecular ion peak at m/e 230.1068 for the chemical formula $C_{12}H_{19}O_2Cl$. The above data suggested that the alcohols were chlorinated at the C-3 position and it therefore appeared that chlorination occurred at a faster rate than the Swern's oxidation.

In the Swern's oxidation process, the complex **65** (Scheme VIII) formed between dimethylsulfoxide and oxalyl chloride or its decomposition product **66** is thought to be the reactive species. The intermediate **66** could be envisaged in this case as the positive chlorine source, which reacted with the enol form of the ketone to give a chloro alcohol which was further oxidized in a normal fashion to give the chlorodiketone **64**. With the knowledge of the correct structure of **64**, the formation of the enone **56** under silyl enol ether formation conditions could easily be seen to be a dehydrochlorination[55,56] reaction.

To gain some insight as to the effect of the reagents employed, further reactions were carried out with the chloro diketone **64**. When heated in triethylamine alone, no observable products were obtained, while a mixture of complex products were obtained in dimethylformamide at 130°C. With a mixture of chlorotrimethylsilane and triethylamine in dimethylformamide at 130°C, the chloro diketone **64** was completely converted to the enone **56** in 20 min. Parallel reactions carried out without chlorotrimethylsilane took two hours to go to completion, while the one without triethylamine took three hours. The above results indicated that the combination of chlorotrimethyl-

# SCHEME VIII



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silane, triethylamine, and dimethylformamide accelerated the dehydrochlorination process.

From the foregoing discussion, the following conclusions could be drawn:

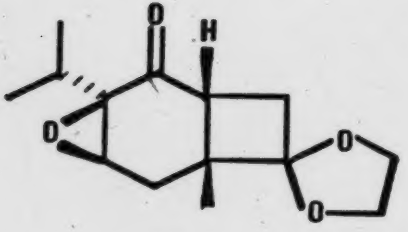
1. The Swern oxidation reagent could also serve as a source of positive chlorine.

2. A combination of chlorotrimethylsilane and triethylamine in dimethylformamide could serve as a dehydrochlorinating agent.

Up to this stage, pipertone (**37**) has been converted to the enone **59** in 30% overall yield by a photocycloaddition with vinyl acetate, hydrolysis, oxidation/chlorination, dehydrochlorination and ketalization. The rest of the synthetic work was carried out with the enone **59**. Having achieved the synthesis of the enone **59**, we set out to explore various possibilities of modifying the cyclohexenone portion of the molecule to the lactone equivalent in dendrobine (**1**). To synthesize an intermediate of the type **39**, we anticipated the use of a 1,3-oxygen transposition reaction to get the ketone oxygen in the right position for the construction of the lactone ring. Several methods are available in the literature for this purpose.[57-62] The well known Wharton reaction[57] was tried first being the most simple of them all. This requires the conversion of the enone **59** to an epoxy ketone followed by the formation of an epoxy hydrazone which can, in principle, rearrange to an allylic alcohol. Oxidation of the allylic alcohol will give an enone of the type **39** as mentioned in the introduction section.

Thus, the enone **59** was treated with 30% hydrogen peroxide and 10% sodium hydroxide in methanol at 0°C. The epoxide **67** was obtained in 92% yield. The ir spectrum showed bands at 1700 and 1245 $cm^{-1}$ due to saturated ketone and epoxide ring respectively. The $^1$Hmr spectrum displayed a doublet (J = 4 Hz) at $\delta$3.44 due to the epoxide methine proton and a singlet at $\delta$1.44 due to the angular methyl group. Two other doublets (J = 7 Hz each) at $\delta$0.92 and 0.84 were assigned to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 252.1262 for the chemical formula $C_{14}H_{20}O_4$. These data corroborated well with the assigned structure **67**. The oxygen of the epoxide was assumed to have been delivered from the less hindered convex side of the molecule.

Upon treatment of the epoxy ketone **67** with hydrazine hydrochloride and acetic acid, the starting material was recovered intact after 24 h. The same reaction was run using 98% ethanol at room temperature and also at reflux. While no reaction was observed at room temperature, decomposition products resulted at reflux temperature.



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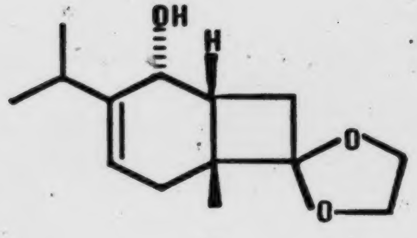

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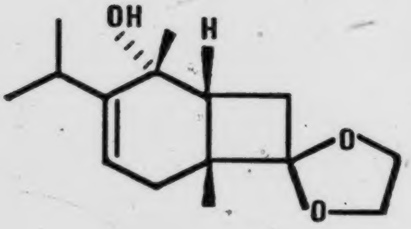

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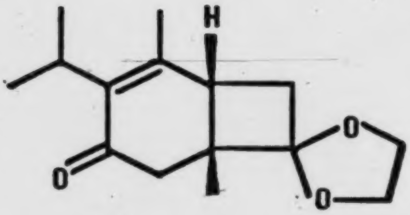

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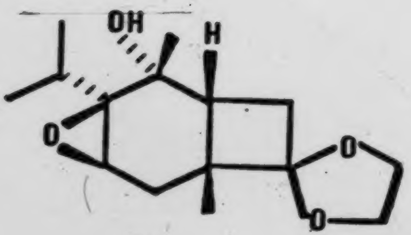

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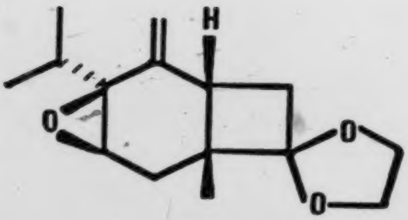

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An alternative method to the Wharton's reaction would be to convert **59** to an allylic alcohol. The hydroxyl group could be converted to a good leaving group and the resulting compound can be used for an $SN_2$' type reaction[58] with a suitable nucleophile to give the required allylic compound with the oxygen functionality transposed. Enone **59** was therefore treated with sodium borohydride in methanol to afford the alcohol **68** in 95% yield. The ir spectrum showed bands at 3440 and 1635 $cm^{-1}$ for the hydroxyl group and the double bond respectively. The $^1$Hmr spectrum displayed a doublet of doublets of doublets (J = J' = 4, J" = 2 Hz) at $\delta$5.50 for the vinylic proton. A broad doublet (J = 5 Hz) at $\delta$4.28 was assigned to the methine proton adjacent to the hydroxyl group. The methine proton of the isopropyl moiety appeared as a septet (J = 7 Hz) at $\delta$2.58. A singlet at $\delta$1.12 and two doublets (J = 7 Hz each) were assigned to the angular and isopropyl methyl groups respectively. A molecular ion peak at 238.1567 for the chemical formula $C_{14}O_{22}O_3$ was exhibited by the mass spectrum. The assigned stereochemistry for the hydroxyl group was based on the assumption that the hydride ion was delivered from the less hindered side of the molecule.

Having obtained the allylic alcohol **68**, the stage was set for the conversion of the alcohol to a good leaving group. It was therefore treated with methanesulfonyl chloride[59] in the presence of triethylamine at 0°C. The product obtained was found to be a diene instead of the desired product. This suggested to us that the allylic mesylate was rather unstable. We suspected that conversion of the alcohol to any good leaving group might give a compound which could suffer the same fate. Other alternatives were therefore examined.

The next alternative was to convert **59** to a tertiary alcohol, which is known to undergo 1,3-oxygen transposition reactions very efficiently.[60] Recently, reports[61-64] of a one carbon functionalized Grignard reagent equivalents, which add to carbonyl groups in a 1,2-fashion, have been published. If the enone **59** could undergo this type of Grignard addition reaction, then application of the above mentioned 1,3-oxygen transposition reaction could give a compound which would possess the right functionalities at carbons 2 and 4 for further elaboration to the lactone moiety. Thus, enone **59** was added to methoxymethoxymethyllithium,[64] generated *in situ* from methoxymethoxymethyl tri-*n*-butylstannane and *n*-butyllithium at -78°C. However, no reaction was observed even when the temperature was raised to -25°C. Since the reagent decomposes above -22°C,[64] the temperature could not be raised any further.

A model reaction using cyclohexanone indicated that the reagent was indeed generated. This fact together with the observation that sodium borohydride reacted rapidly with the enone suggested that the reagent might be too bulky. We therefore decided to investigate whether a methyl group could be added to the ketone moiety of the enone **59**.

Thus the enone **59** was treated with methyllithium in ether at -78°C. The alcohol **69** was obtained in 78% yield. The ir spectrum showed a band at 3500 cm$^{-1}$ due to the hydroxyl group. In the $^1$Hmr spectrum a doublet of doublets (J = 6, J' = 1 Hz) at $\delta$5.50 was assigned to the olefinic proton. Singlets at $\delta$1.18 and 1.10 were assigned to the angular methyl group and the newly introduced methyl group respectively. A doublet at $\delta$1.04 due to the isopropyl methyl groups was also observed. The mass spectrum showed a molecular ion peak at 252.1722 indicating the chemical formula $C_{15}H_{24}O_3$. These spectral data are consistent with the assigned structure **69**. The methyl group was assumed to have been delivered from the less hindered convex side of the molecule.

Treatment of the tertiary allylic alcohol **69** with pyridinium dichromate[65] in dichloromethane afforded the enone **70** in 84% yield. The ir spectrum showed a band at 1665 cm$^{-1}$ indicative of the enone. The $^1$Hmr spectrum showed two singlets at δ1.82 and 1.22 for the olefinic and angular methyl groups respectively, and a doublet at δ1.09 due to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at 250.1470 due to the chemical formula $C_{15}H_{22}O_3$.

The vinylic methyl group needed to be functionalized at this stage. There are literature precedents for the allylic oxidation of α,β unsaturated carbonyl compounds[66,67] using selenium chemistry. It was therefore decided to exploit this reaction to activate the vinylic methyl group in **70**. When the enone **70** was treated with selenium dioxide in refluxing benzene, no reaction was observed. The same reaction performed in refluxing dioxane instead of benzene gave no observable product. Upon exposure to selenium dioxide in the presence of 5% acetic acid in t-butyl alcohol at reflux temperature, only decomposition products were obtained.

At this stage, we decided to add the methyl group to the epoxy ketone **67** to give the epoxy alcohol **71**. Compound **71**, upon dehydration would give the vinyl epoxide **72**. The vinyl group in **72** can be epoxidized to give a diepoxy compound which could undergo a rearrangement reaction with a Lewis acid to a keto aldehyde with the oxygen functionalities at the appropriate positions for further elaboration to the γ-lactone in dendrobine (**1**).

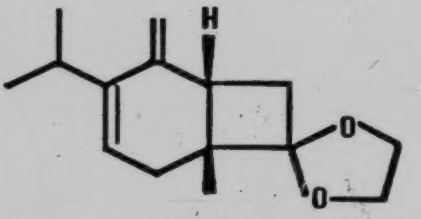
In light of the above discussion, the epoxy ketone **67** was treated with methyllithium in ether at -78°C to give the epoxy alcohol **71** in 67% yield. The ir spectrum showed a band at 3530 cm$^{-1}$ indicating a hydroxyl group. The $^1$Hmr spectrum showed a singlet at $\delta$3.20 for the hydroxyl proton. A doublet (J = 4 Hz) at $\delta$3.16 was attributed to the methine proton of the epoxide ring. Singlets at $\delta$1.24 and 1.22 were assigned to the tertiary and angular methyl groups respectively and two doublets (J = 8 Hz each) at $\delta$1.08 and 0.84 were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 264.1462 indicating the molecular formula $C_{15}H_{20}O_4$. The newly introduced methyl group was assumed to have come from the less hindered convex face of the molecule.

The epoxy alcohol **71** was dissolved in benzene and treated with thionyl chloride in the presence of pyridine.[68] The allylic epoxide **72** was obtained in only 25% yield. The ir spectrum showed bands at 1620 and 1240 cm$^{-1}$ indicative of the olefin and epoxide respectively. The $^1$Hmr spectrum showed the doublets at $\delta$5.74, 5.04 (J = 2 Hz each) and $\delta$3.34 (J = 4 Hz) for the exo methylene and the epoxide protons respectively. The mass spectrum displayed a molecular ion peak at 250.1567 for the chemical formula $C_{15}H_{22}O_3$. Due to the low yield (~25%) obtained in the hydration step we decided to change the reaction sequence, since the allylic epoxide might be unstable under the conditions used.

We intended to add methyllithium to the enone **59** and dehydrate the resulting product before any attempt was made to functionalize the appropriate carbon atoms.

The dehydration method to be used was the pyrolysis[69] of the urethane derivative of an alcohol derived from enone **59**. Thus, the enone **59** in ether at -78°C was treated with methyllithium and the resulting product quenched with p-toluenesulfonyl isocyanate. The crude product obtained was immediately pyrolyzed at 110°C (Kugelrohr oven temperature) at a pressure of 0.5 mm Hg to give a product in 50% yield which showed an olefinic absorption band at 1610 $cm^{-1}$ in the ir spectrum. The $^1$Hmr spectrum displayed a broad triplet (J = 4 Hz) at δ 5.72 due to the proton on the endo double bond and broad singlets at δ4.96 and δ 4.86 due the exo methylene protons. The mass spectrum showed a molecular ion peak at 234.1621 indicating the chemical formula $C_{15}H_{22}O_2$. These data agreed with the assigned structure **73**.

Having obtained diene **73**, attempts were made to functionalize the terminal carbons of the diene selectively. Methods tried were epoxidation,[70] hydroboration,[71,72] and bromination.[32]



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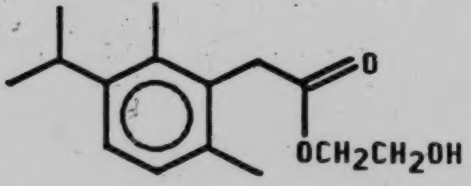

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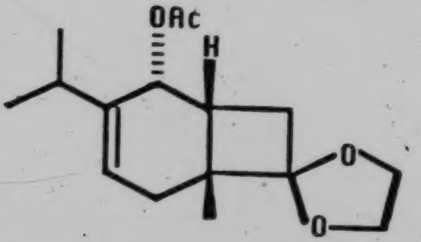

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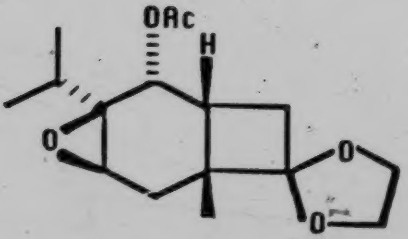

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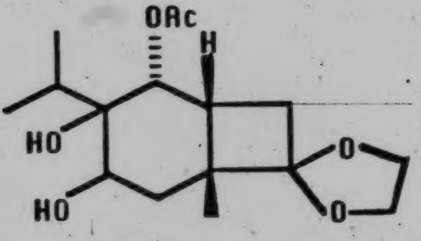

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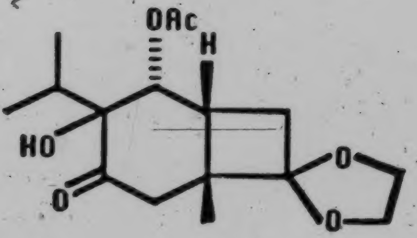

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Treatment of the diene **73** in dichloromethane at 0°C with m-chloroperbenzoic acid gave a very polar compound which exhibited absorption bands at 3600 $cm^{-1}$ and 1725 $cm^{-1}$ due to hydroxyl and carbonyl groups respectively in the ir spectrum. The $^1$Hmr spectrum showed two doublets (J = 8 Hz each) at $\delta$ 7.14 and 7.04 accounting for two vicinal aromatic protons. Two singlets at $\delta$2.30 and $\delta$2.24 were assigned to two aromatic methyl groups, and a doublet at $\delta$1.23 to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at 250.1577 for the chemical formula $C_{15}H_{22}O_3$. These data were consistent with the assigned structure **74**.

When 9-borabicyclo[3.3.1]nonane[71] was used, the starting material was recovered intact, while dibroane[72] gave a complex mixture of products. Molecular bromination[32] also produced a complex mixture of products. An alternative route was called for at this time.

It was decided to go back to use the allylic alcohol **68** and this time around convert it to a less labile leaving group relative to methanesulfonate. The two functional groups we had in mind were either an acetate or an ether. If the alcohol could be converted to any of these two functionalities, then epoxidation followed by

Lewis acid catalyzed rearrangement would give a keto acetate or keto ether.

In the case of a β-keto acetate, elimination of acetate would give the corresponding intermediate of the type **39** needed for the synthesis. Since acetate is a better leaving group than methoxide, this route was the first to be examined. The allylic alcohol **68** was treated with acetic anhydride[73] in pyridine at 0°C to give the allylic acetate **75** in 56% yield. The ir spectrum showed a band at 1735 $cm^{-1}$ corresponding to an ester group. The $^{1}$Hmr displayed a broad triplet (J = 4 Hz) at δ5.66, which was attributed to the methine group adjacent to the acetate, as well as a singlet at δ2.08 for the acetate methyl group. A multiplet at δ5.50 was assigned to the olefinic proton. The mass spectrum showed a moleclar ion peak at 280.1673 indicating the chemical formula $C_{16}H_{24}O_3$. The allylic acetate **75** was then treated with m-chloroperbenzoic acid[70] in dichloromethane to give the epoxide **76** in 72% yield. The ir spectrum exhibited bands at 1737 and 1241 $cm^{-1}$ due to acetate and epoxide respectively. The $^{1}$Hmr spectrum showed two doublets at δ5.48 (J = 6 Hz) and 3.15 (J = 4 Hz) for the methine proton adjacent to the acetate and the epoxide methine proton respectively. Two singlets at δ2.12 and δ1.20 were assigned to the acetate and angular methyl groups. The isopropyl methyl groups appeared as doublets (J = 8 Hz each) at δ0.92 and 0.82. The mass spectrum showed a peak at m/e 253.1443 ($M^+$-43) for the chemical formula $C_{14}H_{21}O_4$.

Epoxides, in the presence of Lewis acids,[74] are known to undergo rearrangement to carbonyl compounds via a 1,2-hydride shift. If the epoxy acetate **76** would undergo such a reaction then further manipulation of the resultant keto acetate would afford an enone of the type **39**. When the epoxy acetate **76** was treated with boron trifluoride etherate in benzene at 0°C, a product, which showed, in the ir spectrum, a hydroxyl absorption at 3460 $cm^{-1}$ with an acetate absorption band at 1734 $cm^{-1}$, was obtained. The $^1$Hmr spectrum exhibited a doublet (J = 6 Hz) at δ5.16 for the methine proton adjacent to the acetate group. Singlets at δ2.00 and 1.18 were assigned to the acetate and angular methyl groups respectively. A doublet (J = 8 Hz) at δ0.89 was attributed to the isopropyl methyl groups. The mass spectrum showed a peak at m/e 255.1594 ($M^+$-59) for the chemical formula $C_{14}H_{23}O_4$. The spectral data corroborates with the structure **77**. The formation of the diol moiety could be due to either moisture in the reaction or an acetate participation in the opening of the epoxide ring-boron trifluoride complex. All attempts made led invariably to the formation of diol **77**. This diol **77** could still be used for the synthetic work if the secondary alcohol was converted to a ketone. The resultant hydroxy acetate could be converted to the required enone of the type **39**. Thus, the diol **77** was treated with pyridinium dichromate in dichloromethane to give the keto alcohol **78** in 83% yield. The ir spectrum showed bands at 3480 $cm^{-1}$ due to a hydroxyl group, at 1735 for the acetate, and at 1710 $cm^{-1}$ indicative of a saturated ketone.The $^1$Hmr spectrum displayed a doublet ($J = 6$ Hz) at $\delta$5.46 for the methine proton adjacent to the acetate group. A singlet at $\delta$2.06 was attributed to the acetate methyl group. The mass spectrum showed an ion peak at m/e 253.1429 ($M^+$-59) for the chemical formula $C_{14}H_{21}O_4$ but the actual molecular weight of m/e 312 was obtained from chemical ionization mass spectroscopy with ammonia.

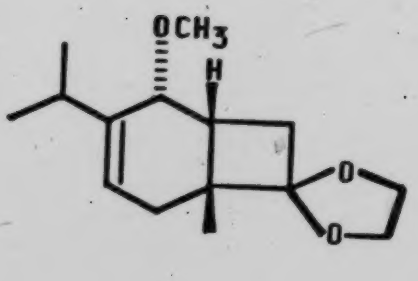
Keto acetates of the type **78** are known to undergo reaction with zinc in acetic acid,[75] to give enones. However, when compound **78** was treated with zinc dust in acetic acid, no reaction occurred even upon heating to a temperature of 75°C overnight.

We next examined the use of an allylic methyl ether instead of the acetate. If hydroboration was done on this allylic ether, an alcohol would be obtained. Oxidation of the alcohol to a ketone followed by elimination of methanol would give the required enone.

Thus the allylic alcohol **68** was treated with sodium hydride in 1,2-dimethoxyethane followed by addition of methyl iodide. The methyl ether **79** was obtained in 81% yield. The ir spectrum displayed an ether absorption at 1098 $cm^{-1}$. The $^1$Hmr spectrum showed singlets at $\delta$5.55 and 3.36 for the olefinic proton and the methyl group of the ether functionality respectively. The mass spectrum exhibited a molecular ion peak at m/e 252.1713 for the chemical formula $C_{15}H_{24}O_3$.

To get an oxygen function at carbon 4 of compound **79**, a hydroboration[71,72] reaction was anticipated. When the methyl ether **79** was treated with diborane in tetrahydrofuran, followed by addition of 30% hydrogen peroxide and 3 N sodium hydroxide, a 3:1 ratio of a mixture of alcohols **80** was obtained. The ir spectrum of the major product showed a band at 3500 $cm^{-1}$ due to the hydroxyl group. The $^1$Hmr spectrum displayed a doublet of doublets (J = 6, J' = 2 Hz) at $\delta$3.48 indicating the proton adjacent to the methoxyl group. A singlet at $\delta$3.20 confirmed the presence of the methoxy group. The mass spectrum showed a molecular ion peak at m/e 270.1831 accounting for the molecular formula $C_{15}H_{26}O_4$.

The minor product displayed a band at 3480 $cm^{-1}$ for an hydroxyl group in the ir spectrum. The $^1$Hmr spectrum displayed a broad doublet (J = 6 Hz) at $\delta$3.64 for the



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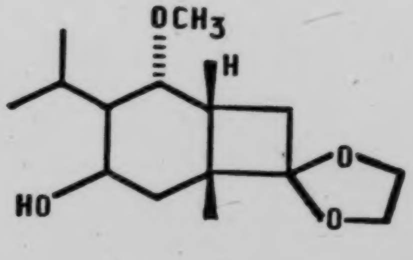

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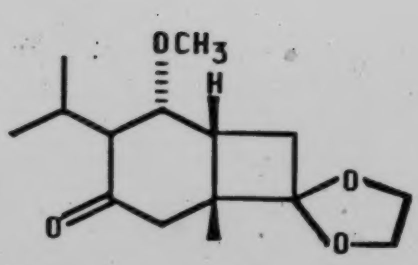

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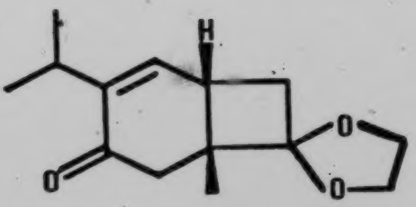

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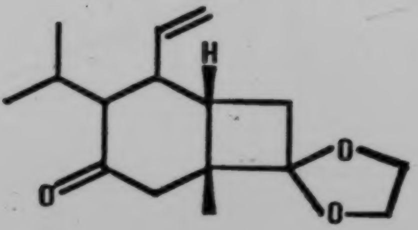

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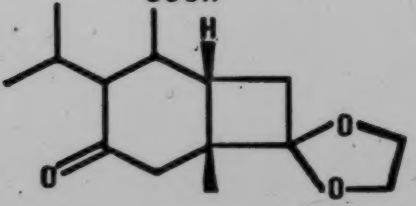


84

methine proton adjacent to the methoxy group. Singlets at $\delta$3.26 and 1.22 were assigned to the methoxy and angular methyl groups respectively. The mass spectrum displayed a peak at m/e 255.1604 ($M^+$-15) for the chemical formula $C_{14}H_{23}O_4$.

The above results indicated that the diborane addition occurred predominantly from one face of the double bond, which was assumed to be the less hindered side. When each of the alcohols **80** was treated with pyridinium dichromate in dichloromethane, only one ketone **81** was obtained in 90% yield. The ir spectrum displayed a band at 1710 $cm^{-1}$ indicating the presence of a saturated ketone. The $^1$Hmr spectrum exhibited a doublet of doublets at $\delta$3.76 (J = 6.5 Hz, J' = 2.5 Hz) which was assigned to the proton adjacent to the methoxy group. A singlet at $\delta$3.28 was attributed to the methoxy group. The mass spectrum showed a molecular ion peak at m/e 268.1675 for the chemical formula $C_{15}H_{24}O_4$.

The stage was set for an elimination reaction. In order to convert the $\beta$-methoxy ketone **81** to the enone of the type **39**, a non-nucleophilic base should be used. A nucleophilic base can also add to the enone formed, in a Michael fashion,[76] and reduce the yield of the reaction. Both 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[77] and 1.8-diazabicyclo[5.4.0]undec-7-ene (DBU)[78] were used as bases. Thus, a benzene solution of compound **81** was refluxed with either of the two bases as a co-solvent to give a single enone **82** in 91% yield. The ir spectrum displayed bands at 1678 and 1615 $cm^{-1}$ indicative of an unsaturated ketone and a double bond respectively. The $^1$Hmr showed three doublets at δ6.45 (J = 5 Hz), 2.56, and 2.16 (J = 16 Hz each) which were assigned to the vinylic proton and the methylene protons α to the ketone respectively. Two other doublets (J = 7 Hz each) at δ1.06 and 1.00 were attributed to the isopropyl methyl groups. The methine proton of the isopropyl moiety appeared as a septet (J = 7 Hz) at δ2.96 while the angular methyl group was a singlet at δ1.24. The mass spectrum displayed a molecular ion peak at m/e 236.1409 indicative of the chemical formula $C_{14}H_{20}O_3$. The preceeding data, especially the coupling patterns of the vinyl and angular methine protons confirmed that indeed the enone **82** was obtained. The enone **82** offers two basic advantages for the construction of the lactone ring. It has an oxygen in the right position for the alcohol portion of the lactone and also the presence of an enone allows for the incorporation of a functionalized one carbon unit equivalent needed for the acid portion.

Grignard reagents[79] are well documented to add to α,β-unsaturated carbonyl compounds in a 1,2-fashion but in the presence of copper ion,[80] the mode of addition is changed predominantly to the 1,4. Since it is the β position of the compound 82 that needs to be functionalized, the latter is the method of choice.

Enone 82 in tetrahydrofuran was added to a solution of cuprous iodide and vinylmagnesium bromide in tetrahydrofuran at -30°C under an argon atmosphere. The ir spectrum of the product obtained showed bands at 1705 and 1640 $cm^{-1}$ indicative of a saturated ketone and a double bond respectively. The $^1$Hmr spectrum showed a doublet of doublets of doublets ($J = 17$, $J' = J'' = 9$ Hz) at $\delta$5.40 for a vinylic proton, two doublets of doublets at $\delta$5.1 ($J = 17$, $J' = 2.5$ Hz) and $\delta$5.08 ($J = 9$, $J' = 2.5$ Hz) due to the methylene protons of the vinyl group. Two doublets ($J = 12$ Hz each) at $\delta$3.10 and 1.80 were assigned to the methylene protons α to the ketone. In the mass spectrum a molecular ion peak at m/e 264.1710 indicated the molecular formula $C_{16}H_{24}O_3$. The foregoing spectral data were consistent with the structure 83.

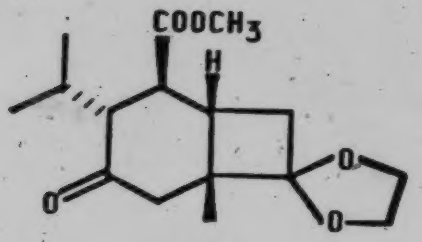
Compound 83 had one carbon more than was needed for the construction of the γ-lactone ring. The vinyl group needed to be reduced by one carbon. Of the various options available for the cleavage of the carbon-carbon double bond,[81-84] ruthenium tetroxide[84] was employed because of its simplicity and the basic conditions normally used. Thus compound **83**, upon treatment with ruthenium tetroxide, gave the acid **84** which was further dissolved in acetone and treated sequentially with potassium carbonate and methyl iodide. The crude product was made up of a mixture of two compounds in a 70:30 ratio ($^1$Hmr analysis). The major product showed bands at 1735 and 1710 cm$^{-1}$ for an ester and saturated ketone respectively. The $^1$Hmr spectrum showed a singlet at $\delta$3.70 due to an ester methyl group. Another singlet at $\delta$1.14 was assigned to the angular methyl group. Two doublets (J = 6 Hz each) at $\delta$1.06 and 0.91 were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at 296.1621 due to the chemical formula $C_{16}H_{24}O_5$.

Decoupling experiments were done on this product to determine the relative stereochemistry of the substituents. Irradiation of the signal at $\delta$1.96 caused the collapse of the doublet of doublets at $\delta$2.30 to a doublet with a coupling constant of 12 Hz. Meanwhile, both doublets at $\delta$1.06 and 0.91 collapsed to singlets. Irradiation of the signal at $\delta$2.30 caused the collapse of not only the doublet of septets at $\delta$1.96 to a septet but also the doublet of doublets at $\delta$3.09 to a doublet with a coupling constant of 12 Hz. These findings strongly suggested that the signal at $\delta$1.96 was due to the isopropyl methine proton, while the one at δ2.30 was due to the C-3 proton α to the ketone and the signal at δ3.09 could be due to the methine proton at C-2. Upon irradiation of the signal at δ3.09 the doublet of doublets of doublets at δ1.76 collapsed to a doublet of doublets and the doublet of doublets at δ2.30 (C-3H) to a doublet with a coupling constant of 3 Hz. These observations confirmed that the signal at δ3.09 was due to C-2H and also suggested that the signal at δ1.76 could be due to C-1H.

Irradiation of the signal at δ2.66 caused the collapse of the doublet of doublets of doublets at δ1.76 to a doublet of doublets ($J$ = 12 Hz, $J'$ = 3 Hz) and the doublet of doublets at δ2.20 to a doublet. These findings suggested that the signals at δ2.66 and 2.20 were due to the methylene protons of the four-membered ring and also confirmed that the signal at δ1.76 was indeed due to the angular methine proton (C-1H). The collapse of a doublet at δ3.02 to a singlet upon irradiation of the signal at δ1.84 and vice versa clearly suggested that those two signals were due to the methylene protons at C-5. The coupling constant of 12 Hz observed for the C-3H upon irradiation of the isopropyl methine proton suggested that the C-3H was coupled to an axial neighboring proton. The coupling constant of 12 Hz obtained for the C-2H upon irradiation of the C-3H again suggested that the C-2 proton bore a diaxial relationship to C-1H. That C-1H and C-2H were axial to each other was confirmed by the observation that the doublet of doublets of doublets for C-1H collapsed to a doublet of doublet ($J$ = 12 Hz, $J'$ = 3 Hz). The bigger coupling constant of 12 Hz was absent when the signal at δ3.09 (C-2H) was irradiated. The foregoing discussion not only showed that the protons at C-1, C-2, and C-3 were axial relative to each other but also suggested that the major product was the keto ester **85**.

The minor isomer showed bands in the ir spectrum at 1740 $cm^{-1}$ and 1700 $cm^{-1}$ indicative of an ester and a ketone respectively. The $^1$Hmr spectrum showed singlets at δ3.94 and 1.24 which were assigned to the ester and angular methyl groups respectively. Two doublets at δ1.00 and 0.82 were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 296.1619 for the chemical formula $C_{16}H_{24}O_5$.

The stereochemistry of the minor isomer was also determined by decoupling experiments. Irradiation of the isopropyl doublets at δ1.00 and 0.82 caused, in each case, the collapse of a doublet of septet at δ1.94 to a doublet of quartets. This clearly suggested that the signal at δ1.94 was due to the methine proton of the isopropyl



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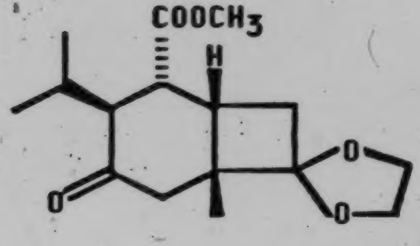

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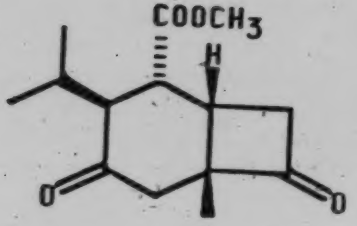

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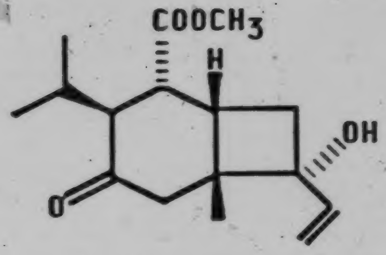

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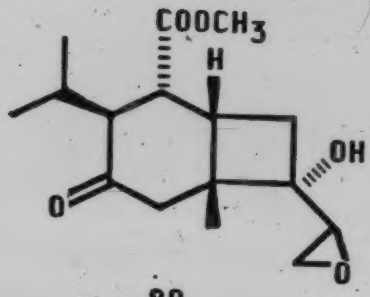

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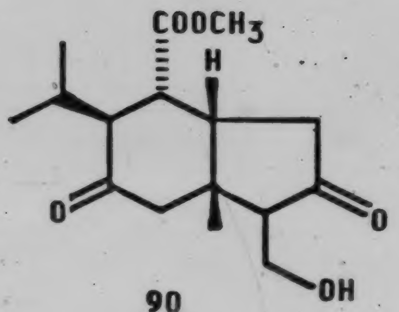


90

group. This was confirmed when both doublets at $\delta$1.00 and 0.82 collapsed to singlets upon irradiation of the signal at $\delta$1.94. Irradiation of the doublet of doublets at $\delta$2.94 led to the collapse of not only the isopropyl methine proton signal at $\delta$1.94 to a septet but also a doublet of doublets at $\delta$4.04 to doublet (J = 4 Hz). This suggested that the signal at $\delta$2.94 was due to the C-3H and that at $\delta$4.04 due to C-2H. Upon irradiating the signal at $\delta$4.04, the doublet of doublets at $\delta$2.94 collapsed to a doublet and the doublet of doublets of doublets at $\delta$2.36 to a doublet of doublets. These observation confirmed that the signals at $\delta$4.04 and 2.94 were due to C-2H and C-3H respectively. It was suggested that the signal at $\delta$2.36 was due to the angular methine proton. Irradiation of the signal at $\delta$2.36 caused the collapse of the doublet of doublets at $\delta$4.04 (C-2H) to a doublet (J = 12 Hz) which suggested that the proton was axially oriented to a neighboring proton. When a signal at 2.16 was irradiated, the doublet of doublets of doublets at $\delta$2.36 collapsed to a broad doublet (J = 4 Hz). This observation confirmed that the signal at $\delta$2.36 was indeed due to C-1H and also gave the coupling constant between C-1H and C-2H to be 4 Hz. Since the coupling constant between C-3H and C2H was 12 Hz, it could be concluded that while C-3H and C-2H bore a diaxial relationship to each other, C-1H had an axialequatorial relationship with C-2H. The foregoing discussion pointed to the structure **86** as the minor isomer.

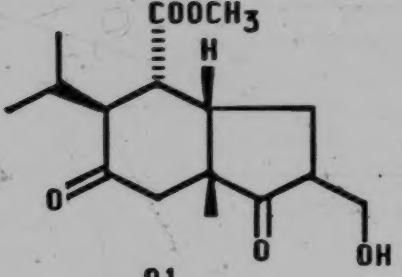
Even though compound **85** could be used for the synthesis by epimerizing the C-2 and C-3 centers at a later stage to the ones required for dendrobine (**1**), the compound **86** was utilized for the rest of the synthetic work since it possessed the right stereochemistry. The keto ester **86**, not only had the right stereochemistry at C-1, C-2, C-3, and C-6 but also a ketone function. This ketone could be used to incorporate a leaving group at C-5 which would be needed for the construction of the pyrrolidine ring. An attempt was made to incorporate a leaving group at this stage at C-5, in the form of a bromide. When the keto ester **86**, in glacial acetic acid, was treated with pyridinium bromide perbromide, a complex mixture of compounds was obtained. Since the decomposition might still be due to the instability of the four-membered ring, it was decided to work on its ring expansion to the five-membered ring.

Treatment of the keto ester **86** with _p_-toluenesulfonic acid in refluxing acetone gave the diketo ester **87** in 72% yield. The ir spectrum showed bands at 1781, 1735 and 1714 $cm^{-1}$ for the four-membered ring ketone, the ester, and the six-membered ring ketone respectively. The $^1$Hmr spectrum displayed two doublets of doublets at δ3.48 (J = 18 Hz, J' = 10 Hz) and 2.86 (J = 18 Hz, J' = 4 Hz) attributed to the methylene protons of the four-membered ring. A doublet of doublets of doublets at δ2.68 (J = 10, J' = 4, J" = 2.5 Hz) was assigned to the angular methine proton. Singlets at δ3.68 and 1.32 were assigned to the ester and angular methyl groups. A septet at δ2.46 (J = 7.5 Hz) and two doublets at δ1.09 and 0.86 (J = 7.5 Hz each) were attributed to the isopropyl methine and methyl groups respectively. The mass spectrum exhibited a molecular ion peak at 252.1357 indicative of the chemical formula $C_{14}H_{20}O_4$.

Having obtained the diketo ester **87**, time was now ripe for the examination of the ring expansion reaction. The direct ring expansion of cyclic ketones with boron trifluoride etherate and ethyl diazoacetate[86-89] is known to proceed by the migration of the less substituted α-carbon predominantly.[87-89] Application of this method to the diketo ester **87** would give a compound which will have an oxygen function at the right position in the five-membered ring to allow further elaboration to the pyrrolidine ring in dendrobine (**1**).

An alternative method for the ring expansion process involved the conversion of **87** to an epoxy alcohol via selective addition of a vinyl group to the four-membered ring ketone (**87**→**88**) followed by epoxidation (**88**→**89**). Acid catalyzed rearrangement of the epoxy alcohol **89** could, in principle, give two compounds **90** and **91** either of which would be useful in the present synthetic endeavor. Compound **90** would be the product obtained by migration of the more substituted carbon atom, while **91** would be obtained by the migration of the less substituted carbon atom. Compound **90** possesses the functionalized one carbon unit for the construction of the pyrrolidine ring in dendrobine (**1**). On the other hand compound **91** could be converted to the same intermediate expected from the diazoacetate ring expansion process. The epoxy alcohol rearrangement route was examined first.

The diketo ester **87** was treated with vinyllithium in tetrahydrofuran at -78°C, to give a single compound **88** in 85% yield. The stereochemistry of the vinyl group was assigned on the assumption that it was delivered from the less hindered side of the ketone. The ir spectrum showed bands at 3444, 1735, 1709 $cm^{-1}$ for hydroxyl, ester, and saturated ketone respectively. The $^1$Hmr spectrum showed doublet of doublets at $\delta$ 6.02, 5.46 and 5.34 for the vinylic protons. Singlets at $\delta$ 3.70 and 1.14 were assigned to the ester and angular methyl groups. Doublets at $\delta$ 0.90 and 0.80 were attributed to the isopropyl methyl groups.



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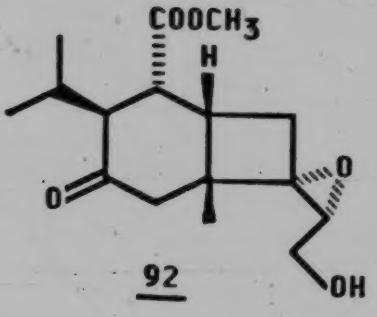

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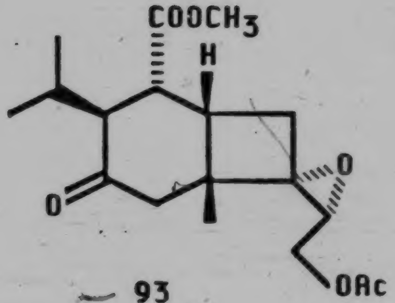

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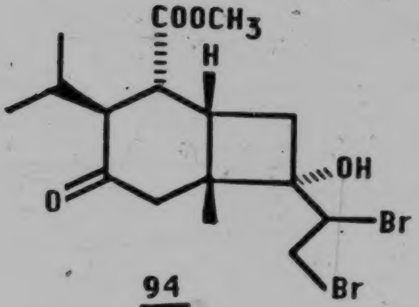

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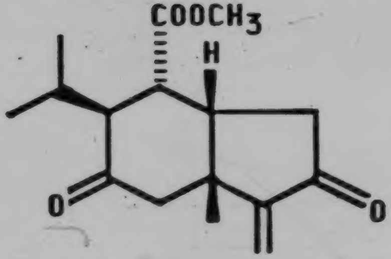

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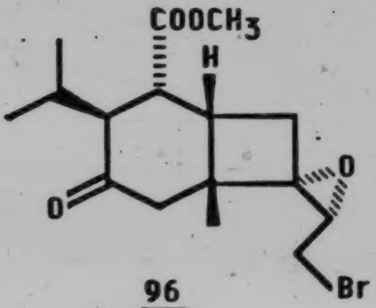

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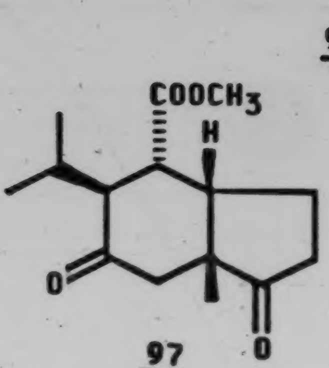

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The mass spectrum showed a molecular ion peak at m/e 280.1660 for the chemical formula $C_{14}H_{24}O_4$.

When the vinyl alcohol **88** was treated with m-chloroperbenzoic acid in dichloromethane at room temperature, two epoxides **89** were obtained in 1:1 ratio in almost quantitative yield. The ir spectrum of one of the epoxides displayed bands at 3461, 1734, 1711 and 1245 $cm^{-1}$ indicative of a hydroxyl, an ester, a ketone, and an epoxide respectively. The $^1$Hmr spectrum exhibited singlets at $\delta$3.72 and 1.16 due to ester and angular methyl groups. Doublets of doublets at $\delta$3.06, and 2.68 (J = 4 Hz, J' = 2.5 Hz each) were attributed to the epoxide methylene protons while a triplet at $\delta$2.88 (J = 4 Hz) was assigned to the epoxide methine protone. Two doublets at $\delta$1.06 and 0.9 (J = 7 Hz each) were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 296.1624 indicative of the chemical formula $C_{16}H_{24}O_5$.

The ir spectrum of the other epoxide displayed bands at 3473, 1734, 1711, and 1245 $cm^{-1}$ indicative of a hydroxyl, ester, ketone and epoxide respectively. The $^1$Hmr spectrum displayed singlets at $\delta$3.72 and 1.16 due to the ester and angular methyl groups respectively. A doublet of doublets at $\delta$3.36 (J = 4 Hz, J' = 2.5 Hz) was assigned to the epoxide methine proton. The mass spectrum displayed a molecular ion peak at m/e 296.1624 indicating the chemical formula $C_{16}H_{24}O_5$. The spectral data indicated the two compounds differed only at the epoxide methine carbon.

With the epoxy alcohol in hand, we then set out to effect the rearrangement. Of the acids[90-92] tried, only stannic chloride gave any identifiable product. Thus, treatment of each of the epoxides **89** with stannic chloride[92] in dichloromethane gave a single compound. The ir spectrum showed bands at 3460, 1734 and 1714 $cm^{-1}$ for hydroxyl, ester, and ketone respectively. The $^1$Hmr spectrum showed a doublet of doublets (J = 7 Hz, J' = 2 Hz) at $\delta$4.00 for a proton adjacent to oxygen. Singlets at $\delta$3.72 and 1.14 were assigned to the ester and angular methyl groups respectively. Two doublets at $\delta$1.04 and 0.84 were attributed to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at 296.1628 for the chemical formula $C_{16}H_{24}O_5$. Since the complexity of the $^1$Hmr spectrum did not allow us to identify the compound obtained, it was conceived that a more simplified spectrum could be obtained upon acetylation of the compound for identification. Upon treatment of the alcohol with acetic anhydride in pyridine, an acetate was obtained. The ir spectrum showed absorption bands at 1735 and 1713 $cm^{-1}$ for esters and ketone respectively. The

$^1$Hmr spectrum showed a doublet of doublets (J = 7, J' = 6 Hz) at δ5.34 for the proton adjacent to the acetate group. Three singlets at δ3.70, 2.12 and 1.08 were attributed to the methyl groups of the ester, acetate and at the angular position respectively. Two doublets at δ1.08 and 0.88 were assigned to the isopropyl methyl groups. The mass spectrum showed a molecular ion peak at m/e 338.1742 for the chemical formula $C_{18}H_{26}O_6$. To gain further insight into the actual structure of the acetate, it was decided that, upon elimination of the acetate, a more simplified spectrum should result. When the compound was refluxed in pyridine only the starting material was recovered. This suggested that the expected ring expansion did not take place during the stannic chloride reaction. If it had, then the acetates of the expected alcohols **90** and **91** should undergo elimination reaction in the presence of a base. Since the acetate obtained did not undergo any reaction upon base treatment it could be concluded that the compound obtained was neither **90** nor **91**. A possible candidate for the product of the acid catalyzed reaction could be the epoxy alcohol **92** and therefore the acetate formed was **93**.

In search of an alternative to the epoxy alcohol **89** rearrangement, it was decided to examine the bromination reaction of the vinyl alcohol **88**. It was anticipated that the bromonium intermediate formed could undergo a ring expansion to give a β-bromo ketone which upon elimination would give an enone required for further elaboration. The vinyl alcohol **88** reacted with molecular bromine to give the dibromide **94**. The ir spectrum showed bands at 3520, 1732, and 1712 $cm^{-1}$ for a hydroxyl, an ester, and a ketone respectively. The $^1$Hmr showed a doublet of doublets (J = 10, J' = 6 Hz) at $\delta$4.44 due to a proton adjacent to a bromide. Singlets at $\delta$3.72 and 1.22 were assigned to the ester and angular methyl groups. Two doublets at $\delta$1.04 and 0.88 were attributed to the isopropyl methyl groups. The mass spectrum showed a peak at m/e 358.0815 for the chemical formula $C_{16}H_{23}O_4Br$. When the dibromide **94** was refluxed in pyridine, it gave a monobromide. Here again under conditions employed, it was expected that, if ring expansion indeed occurred the product obtained would also undergo a dehydrobromination reaction to give an enone **95**. The formation of a monobromide clearly ruled out the fact that a ring expansion process had taken place. The bromide obtained could likely be the epoxy bromide **96**. The vinyl alcohol **88** and the epoxy alcohol **89** are potential precursors to the hydrindane derivative **90**, a potential intermediate to the total synthesis of dendrobine (**1**). Alternatively the diketo ester **87** could be ring expanded with ethyl diazoacetate in the presence of boron trifluoride etherate and decarbomethoxylation of the resulting compound would give the hydrindane derivative 97, also potential intermediate towards the total synthesis. Work towards this end is currently being undertaken.

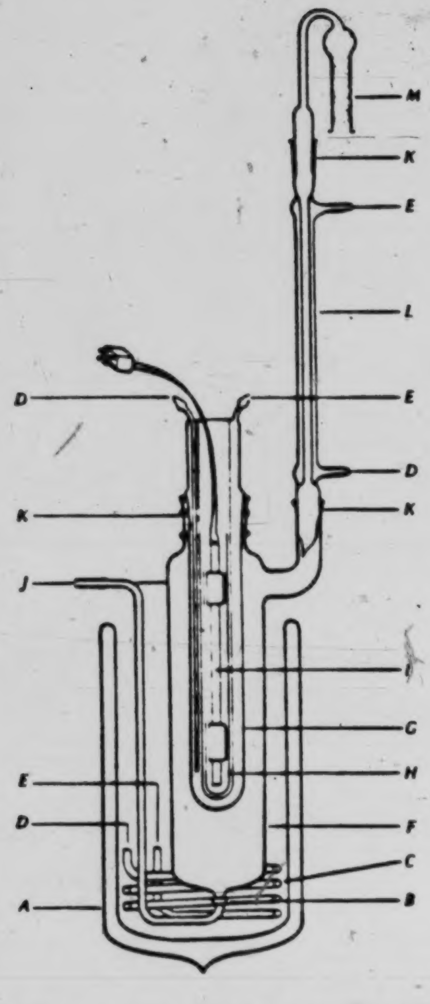


**Figure 2:** *A*, Dewar flask; *B*, sintered glass filter; *C*, metal cooling coil; *D*, water inlet, *E*, water outlet, *F*, reaction vessel, *G*, quartz immersion well; *H*, pyrex filter, *I*, lamp; *J*, nitrogen gas inlet, *K*, ground glass joint, *L*, condenser, *M*, calcium chloride drying tube

# EXPERIMENTAL

## General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Elemental analysis were performed by the microanalytical laboratory of the department. Infrared spectra (ir) were recorded on a Nicolet 7-199 FT-IR spectrophotometer and were obtained on chloroform cast unless otherwise stated. The proton nuclear magnetic resonance ($^1$Hmr) spectra were recorded on a Varian HA-100/Digilab, Bruker W-200 or Bruker W-400 spectrometers and were obtained on solutions in deuterochloroform with tetramethylsilane as the internal standard. Carbon-13 nuclear magnetic resonance spectra ($^{13}$Cmr) were recorded on a Bruker W-200 and W-400 spectrometer and were obtained on deuterochloroform solutions with tetramethylsilane as internal reference. X-ray analysis was performed by Dr. R. Ball of this department. Crystalline samples were recrystallized and liquid samples were subjected to Kugelrohr distillation before submitting for elemental analysis. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and b = broad. Mass spectra (ms) were recorded on a A.E.I. model MS 9, MS 12 or MS 50 mass spectrometer.

## Materials

Benzene, toluene and ether were freshly distilled over lithium aluminum hydride. Tetrahydrofuran was distilled over sodium in the presence of benzophenone. Dichloromethane used for reaction purpose was freshly distilled over calcium hydride, so were triethylamine and chlorotrimethylsilane. Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. 1,1-Diethoxyethene[52] and 2-ethyl-2-methyl-1,3-dioxolane[48] were prepared according to literature procedures. Argon was purified by passing it through a train of gas wash bottles containing sequentially, Fieser's solution,[85] conentrated sulfuric acid, and potassium hydroxide pellets.

## 6-Isopropyl-3-methylcyclohex-2-en-1-one (**37**)

At -78°C, a solution of 6-isopropyl-3-methylanisole (93.48 g, 0.57 mol) in ether (500 mL) and *t*-butyl alcohol (500 mL) was added over a period of 50 min to freshly distilled ammonia (1.1 L) under argon atmosphere. Lithium metal (64.35 g, 9.3 g-atom) was added in small portions over a period of 40 min. The resulting blue solution was stirred for 5 h, after which period the blue color was discharged. Methanol (500 mL) was then added dropwise and the ammonia allowed to evaporate at room temperature overnight. Water (2 L) was added and the resulting mixture extracted with ether (4 x 500 mL). The combined ether extracts were washed with saturated aqueous sodium chloride solution and concentrated to a volume of about 100 mL. To this solution were added methanol (750 mL), water (80 mL), and concentrated hydrochloric acid (15 mL). The mixture was heated to reflux for 1 h under an argon atmosphere. The resulting solution was concentrated to a volume of *ca*. 200 mL and diluted with water (300 mL). It was then extracted with dichloromethane (3 x 500 mL). The dichloromethane layer was dried over magnesium sulfate, filtered, and concentrated to give the crude product which was distilled under reduced pressure to give 6-isopropyl-3-methylcyclohex-2-en-1-one **37** (71.8 g, 83% yield): b.p. 75°C/8 mm Hg; ir 1670 and 1620 $cm^{-1}$ (enone C=O and C=C); $^1$Hmr $\delta$ 5.80 (m, 1H, $-\overset{|}{C}=CH-$), 1.98 (s, 3H, $CH_3\overset{|}{C}=$), 1.00 and 0.86 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 152.1200 (calcd. for $C_{10}H_{16}O$: 152.1219).

### (1R*,6R*,7S*)- (**42**) and (1R*,6R*, 7R*)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (**43**)

A mixture of 6-Isopropyl-3-methyl-2-cyclohexen-1-one **36** (20 g, 0.132 mol) and vinyl acetate (156.9 g, 1.87 mol) in benzene (800 mL) were placed in the reaction vessel shown in Fig. 2 (Page 82). The reaction mixture was exposed to a constant flow of argon. The solution was irradiated with a 450 W Hanonia high pressure mercury-vapor quartz lamp using a Pyrex filter while cooling the reaction vessel with crushed ice and water in a Dewar flask. The solution was concentrated after 24 h and the resulting viscous colorless oil was dissolved in dry benzene (300 mL). 1,5-Diazabicyclo[5.4.0]undec-5-ene (19.5 g, 0.132 mol) was added to the solution and heated to reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated. Column chromatography of the residue on silica gel with 5% ether in petroleum ether gave pure ketone **42** (3.12 g, 10% yield) as a colorless oil: ir 1739 (ester C=O) and 1705 cm$^{-1}$ (ketone C=O); $^1$Hmr $\delta$4.86 (d, 1H, J = 10 Hz, $-\overset{|}{C}HO-$), 2.08 (s, 3H, $-OCOC\underline{H}_3$), 1.22 (s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), 0.96, and 0.86 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms m/e 196.1454 (M$^+$-42; calcd. for $C_{12}H_{20}O_2$: 196.2770) and 154.1314 (M$^+$-84; calcd. for $C_{10}H_{18}O$: 154.1340). Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; Found: C, 70.31, H, 9.17.

Further elution with 10% ether in petroleum-ether gave a mixture of ketones **42** and **43** (8.15 g, 26% yield) in a 1:3 ratio (by $^1$Hmr analysis).

Continued elution with 10% ether in petroleum-ether gave pure ketone (**43**) (9.15 g, 29% yield): ir 1740 (ester

C=O) and 1720 cm$^{-1}$ (ketone C=O); $^1$Hmr δ4.74 (t, 1H, J = 9 Hz, $-\overset{|}{C}HO-$), 2.02 (s, 3H, $-OCOCH_3$), 0.96 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 0.90 and 0.86 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms M$^+$ 238.1568 (calcd. for $C_{14}H_{22}O_3$: 238.1570).

### (1R*,6R*,7S*)- (**45**) and (1R*,6R*,7R*)-7-Hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (**46**)

To a solution of keto acetate **42** (99 mg, 0.42 mmol) in 50% aqueous methanol (5 mL), was added potassium carbonate (70 mg, 0.51 mmol). The resulting mixture was refluxed under argon for 1 h, and cooled to room temperature. Water was added to it and the resulting mixture extracted with methylene chloride. The organic extracts were dried, filtered and concentrated. Flash column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave alcohol **45** (82 mg, 100% yield): ir 3389 (-OH) and 1700 cm$^{-1}$ (C=O); $^1$Hmr δ4.12 (br d, 1H, J = 8.5 Hz, $-\overset{|}{C}\underline{H}OH$), 2.36 (quintet, 1H, J = 8 Hz, $-C\underline{H}(CH_3)_2$), 0.92 (s, $-\overset{|}{\underset{|}{C}}HC\underline{H}_3$), 0.84, and 0.80 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms M$^+$ 196.1464 (calcd. for $C_{12}H_{20}O_2$: 196.1464). *Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; Found: C, 73.29; H, 10.18.

Hydrolysis of keto ester **43** (1.2 g, 5 mmol) under the same conditions as above gave the keto alcohol **46** (986 mg, 100% yield); ir 3380 (-OH) and 1701 cm$^{-1}$ (C=O); $^{1}$Hmr δ4.02 (t, 1H, J = 8 Hz, $-\overset{|}{C}\underline{H}OH$), 1.16 (s, $-\underset{|}{\overset{|}{C}}CH_3$), 0.80 and 0.78 (both d, 3H each, J = 8 Hz, $-CH(C\underline{H_3})_2$; ms M$^+$ 196.1465 (calcd. for $C_{12}H_{20}O_2$: 196.1464). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; Found: C, 73.24; H, 10.39.

## (1R*,6R*,7R*)-7-Acetoxy-3-bromo-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (**47**)

To the keto acetate **43** (205 mg, 0.86 mmol) was added glacial acetic acid (4 mL) with stirring at room temperature under an argon atmosphere. Pyridinium bromide perbromide (331 mg, 1.03 mmol) was then added to the mixture and stirred overnight. The mixture was then neutralized with ice cold saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave the bromo acetate **47** (68.1 mg, 25%); ir 1746 (acetate C=O) and 1725 cm$^{-1}$ (ketone C=O); $^{1}$Hmr δ4.88 (dt, 1H, J = 8, J' = 1 Hz, $-\overset{|}{C}HOCO-$), 2.96 (ddd, 1H, J = 10, J' = 5, J" = 1 Hz $-\overset{|}{C}HCO-$), 2.08 (s, 3H, $-OCOCH_3$), 1.3 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.18 and 1.02 (both d, 3H each, J = 8 Hz each $-CH(C\underline{H}_3)_2$; ms M$^+$ 316.0632 and 318.0613 (calcd. for $C_{14}H_{21}O_3Br$: 316.0674 and 318.0654).

Further elution gave the dibromide **48** (88 mg, 26% yield); ir 1745 (acetate (C=O) and 1720 cm$^{-1}$ (ketone C=O); $^1$Hmr $\delta$ 4.84 (dd, 1H, J = 16 Hz, J' = 8 Hz, $-\overset{|}{C}HOCO-$), 3.23 (dd, 1H, J = 12 Hz, J' = 8 Hz, C-8H), 2.01 (s, 3H, $-OCOCH_3$), 1.24 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.12 and 0.96 (both d, 3H, each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms m/e 315.0596 and 317.0577 (M$^+$-79; calcd. for $C_{14}H_{20}O_3Br$: 315.0596 and 317.0576).

### (1R*,6R*,7R*)-7-Acetoxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-3-en-2-one (**49**)

A pyridine (4 mL) solution of the bromo acetate **47** (201 mg, 0.63 mmol) was refluxed under an argon atmosphere for 4 h. The solution was cooled to room temperature and made acidic with ice cold 1 N hydrochloric acid. The resulting mixture was then extracted with dichloromethane (4 x 15 mL), dried, filtered, and concentrated. Column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave the enone acetate **49** (139 mg, 94% yield); ir 1744 (acetate C=O), 1670 (enone C=O), and 1640 cm$^{-1}$ (enone C=C); $^{1}$Hmr δ6.64 (t, 1H, J = 4 Hz, $-CH{=}\overset{|}{C}CO-$), 4.94 (t, 1H, J = 8 Hz, $-\overset{|}{C}HOCO-$), 3.1 (dd, 1H, J = 12, J' = 8 Hz, $-\overset{|}{C}HCO-$), 2.1 (s, 3H, $-OCOCH_3$), 1.34 (s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), 1.1, and 1.06 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); $^{13}$Cmr δ: 199.9 (ketone C=O), 170.7 (acetate C=O), 144.8 (C-3), 139.8 (C-4), and 71.5 (C-7); ms M$^+$ 236.1468 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

### (1R*,6R*,7R*)-7-Hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-3-en-2-one (**50**)

Aqueous methanol (5 mL) was added to the enone acetate **49** (175 mg, 0.74 mmol). Potassium carbonate (123 mg, 0.89 mmol) was then added to the resulting mixture and refluxed for 1 h. The reaction mixture was allowed to cool to room temperature. It was then acidified and resulting mixture extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. Flash column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave the enone alcohol **50** (143 mg, 100% yield); ir 3440 (-O-H), 1660 (C=O), and 1640 cm$^{-1}$ (C=C): $^{1}$Hmr δ6.56 (ddd, 1H, J = 6, J' = 3, J" = 1 Hz, $-CH{=}\overset{|}{C}CO-$), 4.26 (6t, 1H, J = 7 Hz, $-\overset{|}{C}\underline{H}OH$), 2.96 (septet, 1H, J = 7 Hz, $-C\underline{H}(CH_3)_2$), 1.28 (s, 1H, $-\underset{|}{\overset{|}{C}}CH_3$), 1.04, and

1.00 (both d, 3H each, J = 7 Hz each, $-\text{CH}(\text{C}\underline{\text{H}}_3)_2$); ms M$^+$ 194.1309 (calcd. for $C_{12}H_{18}O_2$: 194.1307).

### (1R*,6R*,7R*)-7-Acetoxy-1-bromo-3-isopropyl-6-methylbicyclo[4.2.0]oct-3-en-2-one (**51**)

The dibromo acetate **48** (59 mg, 0.01 mmol) in pyridine (1 mL) was refluxed under argon for 1 h. The solution was cooled to room temperature and solvent evaporated under reduced pressure. Column chromatography of the residue on silica gel, eluting with 5% ethyl acetate in petroleum ether gave the enone **51** (41 mg, 87% yield); ir 1744 (acetate C=O) and 1660 cm$^{-1}$ (enone C=O); $^1$Hmr $\delta$6.50 (bt, 1H, J = 4 Hz, $-\text{CH}=\overset{|}{\text{C}}\text{CO}-$), 4.85 (dd, 1H, J = 10; J' = 7 Hz, $-\overset{|}{\text{C}}\text{HOCO}-$), 2.08 (s, 3H, $-\text{OCOCH}_3$), 1.32 (s, 3H, $-\underset{|}{\overset{|}{\text{C}}}\text{CH}_3$), 1.10 and 1.00 (both d, 3H each, J = 8 Hz each, $-\text{CH}(\text{C}\underline{\text{H}}_3)_2$); ms M$^+$ 314.0516 and 316.0502 (calcd. for $C_{14}H_{19}O_3Br$: 314.0517 and 316.0497).

### 5-Isopropyl-2-methyl-7-oxabicyclo[4.3.0]-octa-1,3,5-trien-8-ol (**52**)

Potassium carbonate (110 mg, 0.80 mmol) was added to a mixture of the enone bromide **51** (210 mg, 0.66 mmol) and a 1:1 mixture of methanol and water (5 mL). The resulting mixture was refluxed for 1 h. It was then cooled to room temperature, acidified with ice cold hydrochloric acid, and extracted with chloroform (4 x 10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Purification of the residue obtained on silica gel column, eluting with 10% ethyl acetate in petroleum ether, gave the lactol (119 mg, 94% yield); ir 3444 (-OH), 1620, 1610, 1580, 923 $cm^{-1}$ (aromatic C=C); $^1$Hmr $\delta$7.04, 6.74 (both d, 1H each, J = 8 Hz each, C-3H and C-4H), 6.13 (dd, 1H, J = 8, J' = 2 Hz, $-\overset{|}{C}\underline{H}OH$), 3.32 (dd, 1H, J = 12, J' = 8 Hz, Ar-C$\underline{H}$HCO-), 3.12 (septet, 1H, J = 8 Hz, -C$\underline{H}$($CH_3$)$_2$), 2.96 (dd, 1H, J = 12, J' = 2 Hz, ArCH$\underline{H}$CO-), 2.2 (s, 3H, Ar-C$\underline{H_3}$), and 1.24 (d, 6H, J = 8 Hz, -CH(C$\underline{H_3}$)$_2$); ms $M^+$ 192.1148 (calcd. for $C_{12}H_{16}O_2$: 192.1151).

### (1R,6R*,7S*)-7-Acetoxy-3-bromo-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (**53**)

The keto acetate **42** (114 mg, 0.47 mmol), dissolved in glacial acetic acid (2 mL), was treated with pyridinium bromide perbromide (184 mg, 0.57 mmol) under an argon atmosphere overnight. The mixture was then poured into ice cold saturated aqueous sodium bicarbonate and extracted with dichloromethane (4 x 10 mL). The combined organic extracts were washed with water, dried over sodium sulfate, filtered, and concentrated. Purification by column chromatography on silica gel of the residue, eluting with 5% ethyl acetate in petroleum ether gave **53** (35 mg, 23% yield); ir 1740 (acetate and 1710 cm$^{-1}$ (ketone C=O); $^1$Hmr 4.95 (d, 1H, J = 9 Hz, $-\overset{|}{C}HO-$), 2.1 (s, 3H, $-OCOCH_3$), 1.26 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.04 and 0.96 (both d, 3H each, J = 8 Hz, $-CH(\underline{CH_3})_2$); ms M$^+$ 316.0642 and 318.0614 (calcd. for $C_{14}H_{21}O_3Br$: 316.0674 and 318.0654).

## (1R*,6R*,7S*)-7-Acetoxy-3-isopropyl-6-methylbicyclo-[4.2.0]oct-3-en-2-one (**54**)

The bromo acetate **53** (149 mg, 0.47 mmol) was dissolved in pyridine (3 mL) and refluxed for 3 h. The reaction mixture was then cooled to room temperature and acidified with ice cold 1 N hydrochloric acid. The mixture was extracted with dichloromethane (4 x 10 mL) and the combined extracts dried over magnesium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether, to give the enone acetate **54** (100 mg, 90% yield): ir 1743 (acetate C=O) and 1665 cm$^{-1}$ (enone C=O): $^1$Hmr $\delta$ 6.58 (bd, 1H, J = 4 Hz, $-CH=\overset{|}{C}CO-$), 5.08 (d, 1H, J = 8 Hz, $-\overset{|}{C}HOCO-$), 4.16 (septet, 1H, J = 8 Hz, $-\underline{CH}(CH_3)_2$), 2.08 (s, 3H, $-OCOCH_3$), 1.24 (s, 3H,

$-\overset{|}{\underset{|}{C}}CH_3$), 1.04 and 1.00 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 236.1464 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

## (1R*,6R*)-3-Isopropyl-6-methylbicyclo[4.2.0]oct-3-ene-2,7-dione (**56**)

To a solution of alcohol **55** (119 mg, 0.6 mmol) in dimethylsulfoxide (1.8 mL), was added acetic anhydride (1.1 mL). The mixture was kept at 7°C overnight. After that period, water (5 mL) was added and the resulting solution was stirred at room temperature for 30 min. Ice-cold 2 N aqueous sodium hydroxide (5 mL) was added. the mixture was extracted with dichloromethane (4 x 10 mL), dried over magnesium sulfate, filtered and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, afforded the enone **56** (82 mg, 70% yield); ir 1782 (ketone C=O), 1670 $cm^{-1}$ (enone C=O); $^1$Hmr $\delta$6.50 (ddd, 1H, J = 6, J' = 2.5, J" = 1 Hz, $-CH=\overset{|}{C}CO-$), 3.60 (dd, 1H, J = 17.5, J' = 10 Hz, C-8H), 3.00 (dd, 1H, J = 10, J' = 5 Hz, C-1H), 2.84 (dd, 1H, J = 17.5, J' = 5 Hz, C-8H), 2.64 (dd, 1H, J = 19, J' = 6 Hz, $-\overset{|}{C}=CHC\underline{H}H-$), 2.14 (dt, 1H, J = 19, J' = 2.5 Hz, $-\overset{|}{C}=CHCH\underline{H}-$), 1.33 (s, 1H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.08, and 0.98

(both d, 3H each, J = 7 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 192.1150 (calcd. for $C_{12}H_{16}O_2$: 192.1150).

### (1R*,6R*)-3-Isopropyl-6-methylbicyclo[4.2.0]octane-2,7-dione (**57**)

Acetic anhydride (1.9 mL) was added to a solution of a mixture of alcohols **45** and **46** (202 mg, 1.03 mmol) in dimethylsulfoxide (2.9 mL). The reaction mixture was kept at 5°C for four days. Water (5 mL) was added to the resulting solution and stirred at room temperature for 1 h. Ice cold 2 N aqueous sodium hydroxide (5 mL) was added. The mixture was extracted wtih dichloromethane (4 x 10 mL), dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting 20% ethyl acetate in petroleum ether afforded the diketone **57** (120 mg, 60% yield); ir 1782 (four-membered ring ketone) and 1700 $cm^{-1}$ (six-membered ring ketone); $^1$Hmr $\delta$3.48; 3.42 (dd, 1/10H, J = 18, J' = 11.5 Hz; dd, 9/10H, J = 18, J' = 10.5 Hz, C-7H), 3.00; 3.26 (dd, 1/10H, J = 18, J' = 6 Hz; dd, 9/10H, J = 18, J' = 6 Hz, C-7H), 2.74; 2.76 (dd, 1/10H, J = 11.5, J' = 6 Hz; dd, 9/10H, J = 10.5, J' = 6 Hz, C-1H); ms $M^+$ 194.1306 (calcd. for $C_{12}H_{18}O_2$: 194.1307). Anal. Calcd. for

$C_{12}H_{18}O_2$: C, 74.17; H, 9.34. Found: C, 73.82; H, 8.96.

### 7,7-Diethoxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (62)

A mixture of 6-isopropyl-3-methyl-2-cyclohexen-1-one **37** (18.5 g, 0.122 mol) and 1,1-diethoxyethene, (204.7 g, 1.76 mol) in benzene (750 mL) were placed in the reaction vessel. The solution was irradiated with a 450 W Hanovia high pressure mercury-vapor quartz lamp using a Pyrex filter with a constant agitation of the reaction mixture with a steady flow of argon. The reaction mixture was cooled with crushed ice and water during the whole period of irradiation. After 24 h benzene was removed under reduced pressure. Excess 1,1-diethoxyethene was removed by distillation at 70°C/20 Torr. Bulb-to-bulb distillation (75°C/0.25 Torr) of the residue gave the photoadduct mixture **62** (26.1 g, 80% yield); ir 1721 and 1706 $cm^{-1}$ (ketone C=O); $^1$Hmr $\delta$ 3.7-3.44 (m, 4H, $-OC\underline{H_2}CH_3$), 1.34-1.20 (m, 9H, $-OCH_2C\underline{H_3}$ and $-\overset{|}{\underset{|}{C}}CH_3$); ms $M^+$ 268.2032 (calcd. for $C_{16}H_{28}O_3$: 268.2039).

### 3,8-Dibromo-3-isopropyl-6-methylbicyclo[4.2.0]octa-2,7-dione (**63**)

To a mixture of the diketone **48** (99 mg, 0.51 mmol) and glacial acetic acid (2 mL) was added pyridinium bromide perbromide (196 mg, 0.61 mmol) with stirring at room temperature. After 2 h the reaction mixture was extracted with dichloromethane (3 x 10 mL) and the organic layer shaken with sodium bicarbonate solution. Column chromatography on silica gel, eluting with 5% ethyl acetate in hexane, gave the dibromide **63** (82.5 mg, 46% yield); ir 1794, 1774 (four membered C=O) and 1746, 1719 (six membered C=O); $^1$Hmr $\delta$ 5.58 (d, ½ H, J = 10 Hz, -CHBrCO-), 4.80 (d, ½ H, J = 6 Hz, -CHBrCO-), $\delta$ 3.48 (d, ½ H, J = 10 Hz, $-\overset{|}{C}HCO-$), 3.38 (d, ½ H, J = 10 Hz, $-\overset{|}{C}HCO-$), 3.38 (d, ½ H, J = 6 Hz, $-\overset{|}{C}HCO-$), 1.62 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.26 and 0.92 (both d, 3H each, J = 6 Hz each, $-CH(\underline{CH_3})_2$); ms m/e 270.0236 and 272.0230 ($M^+$-80; calcd. for $C_{12}H_{15}BrO$: 270.0255 and 272.0235).

### 5-Isopropyl-2-methyl-7-oxabicyclo[4.3.0]octa-1,3,5-trien-8-one (**58**)

The dibromide **63** (119 mg, 0.34 mmol) was dissolved in pyridine (3 mL) and refluxed under argon for 2 h. The reaction mixture was cooled to room temperature and ice cold 1 M hydrochloric acid was added to the cooled mixture until it was acidic to litmus. It was then extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, filtered and concentrated. Column chromatography on silica gel, eluting with 2% ethyl acetate in petroleum ether, gave the lactone **58** as a light yellow solid (61 mg, 95% yield); mp: 77-79°C; ir 1807 (lactone C=O), 1640, 1625 and 1600 $cm^{-1}$ (aromatic C=C); $^1$Hmr $\delta$7.14, 6.92 (both d, 2H each, J = 8 Hz each, C-3H, C-5H), 3.62 (s, 2H, Ar-$C\underline{H}_2$-CO-), 3.17 (quintet, 1H, J = 7 Hz, $ArC\underline{H}(CH_3)_2$), 2.3 (s, 3, $ArCH_3$), and 1.26 (d, 6H, J = 7 Hz, $ArCH(C\underline{H}_3)_2$); ms $M^+$ 190.0991 (calcd. for $C_{12}H_{14}O_2$: 190.0994).

### (1R*,3S*,6R*)-3-Chloro-3-isopropyl-6-methylbicyclo[4.2.0]octane-2,7-dione (**64**)

A solution of dimethyl sulfoxide (1.35 mL, 0.017 mol) in dichloromethane (5 mL) was added dropwise to a solution of oxalyl chloride (0.826 mL, 0.009 mol) in dichloromethane at -78°C under an argon atmosphere. The mixture was stirred for 15 min after the addition and a dichloromethane (5 mL) solution of the keto alcohol **46** (563 mg, 0.0029 mol) was added dropwise at -60°C. The mixture was allowed to warm up to 0°C at which time triethylamine (6 mL) in dichloromethane (6 mL) was added dropwise and the reaction mixture was allowed to warm up to room temperature. It was then poured into ice cold water (200 mL) and the organic layer separated, washed with water, dried, filtered and concentrated. The residue was purified by column chromatography using 5% ethyl acetate in petroleum ether to afford diketone **64** (588 mg, 89% yield) as a white solid which was recrystallized from hexane: m.p. 60-61°C; ir 1779 (four-membered C=O) and 1709 $cm^{-1}$ (six-membered C=O); $^1$Hmr $\delta$3.64 (dd, 1H, J = 18 Hz, J' = 11.5 Hz, C-8H), 3.14 (dd, 1H, J = 11.5 Hz, J' = 5.5 Hz, C-1H), 2.98 (dd, 1H, J = 18 Hz, J' = 5.5 Hz, C-8H), 2.62 (septet, 1H, J = 7 Hz, $-C\underline{H}(CH_3)_2$) 1.37 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.12 and 0.9 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H_3})_2$); $^{13}$Cmr $\delta$: 211.8 (C-2), 203.4 (C-7), 76.2 (C-3), 64.4 (C-6), 49.4 (C-8), 41.8 (C-1), 33.7 ($-\underline{C}H(CH_3)_2$), 28.1 (C-4), 25.73 (C-5), 23.08 ($-\overset{|}{\underset{|}{C}}\underline{C}H_3$), 18.4 and 17.08 ($-CH(\underline{C}H_3)_2$); m/s $M^+$ 228.0924 and 230.0897 (calcd. for $C_{12}H_{17}ClO_2$: 228.0981 and 230.0888). Anal. Calcd. for $C_{12}H_{17}ClO_2$: C, 63.15; H, 7.51. Found: C, 63.24; H, 7.38.

## 1R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-6-methylbicyclo-[4.2.0]oct-3-en-2-one (**59**)

*p*-Toluenesulfonic acid monohydrate (0.51 g, 0.78

mmol) was added to dry benzene (30 mL) and refluxed, using a Dean-Stark apparatus, with azeotropic removal of benzene-water admixture (~25 mL). 2-Methyl-2-ethyl-1,3-dioxolane (10 mL) was added to the reaction flask together with a toluene solution of enone (**60**) (0.57 g, 3.0 mmol). The mixture was refluxed under an argon atmosphere for 16 h. The cooled reaction mixture was diluted with benzene, washed successively with 5% aqueous sodium bicarbonate and water, dried over sodium sulfate and concentrated to dryness. Column chromatography on silica gel using 10% ether in benzene gave compound **59** (0.51 g, 72% yield): ir 1670 (enone C=O) and 1618 $cm^{-1}$ (enone C=C); $^1$Hmr $\delta$ 6.56 (t, 1H, J = 6 Hz, $-C\underline{H}=\overset{|}{C}CO-$), 3.92 (m, 4H, $-OCH_2CH_2O-$), 1.24 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.24 and 1.00 (both s, 3H each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 236.1410 (calcd. for $C_{14}H_{20}O_3$: 236.1410).

## (1R*,3R*,4R*,6R*)-3,4-Epoxy-7,7-ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-2-one (**67**)

The enone **59** (71 mg, 0.3 mmol) was dissolved in methanol (2 mL). 30% Hydrogen peroxide (0.15 mL) and then 10% sodium hydroxide (0.15 mL) were added and the solution stirred at room temperature for 1 hr. The reaction mixture was poured into water (10 mL) and extracted with ether (3 x 10 mL). The combined extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave the epoxy ketone **67** (70 mg, 92% yeild); ir 1700 (ketone C=O) and 1245 $cm^{-1}$ (epoxide); $^1$Hmr $\delta$3.9 (m, 4H, $-OCH_2CH_2O-$), 3.44 (d, 1H, J = 4 Hz, -CHO-), 1.44 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 0.92 and 0.84 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 252.1364 (calcd. for $C_{14}H_{20}O_4$: 252.1362).

### (1R*,2R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-3-en-2-ol (**68**)

To a solution of enone **59** (105 mg, 0.44 mmol) in methanol (5 mL) was added sodium borohydride (52 mg, 1.32 mmol) at 0°C. The mixture was stirred under argon atmosphere for 30 min and poured into ice-cold saturated aqueous ammonium chloride solution. It was then extracted with dichloromethane (4 x 10 mL). The combined extracts were washed with an aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated. The crude alcohol obtained was purified by flash column chromatography on silica gel using 20% ethyl acetate in petroleum ether to give alcohol **68** (99 mg, 95% yield) as a single compound: ir 3440 (-OH) and 1635 cm$^{-1}$ (C=C); $^{1}$Hmr δ5.50 (ddd, 1H, J = J' = 4 Hz, J" = 2 Hz, $-\overset{|}{C}=CH-$), 4.28 (br d, 1H, J = 5 Hz, $-\overset{|}{C}\underline{H}OH$), 3.86 (m, 4H, $-OCH_2CH_2O-$), 2.58 (septet, 1H, J = 7 Hz, $-C\underline{H}(CH_3)_2$), 1.12 (s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), 1.1 and 1.06 (both d, 3H each, J = 7 Hz, $-CH(C\underline{H_3})_2$); ms M$^{+}$ 238.1567 (calcd. for $C_{14}H_{22}O_3$: 238.1570).

## (1R*,2R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-2,6-dimethylbicyclo[4.2.0]oct-3-en-2-ol (**69**)

Ether (2 mL) was added to the enone **59** (38 mg, 0.16 mmol) at -78°C under an argon atmosphere. Methyllithium (1.6 M, 0.19 mmol) was added to the resulting solution via a syringe. The mixture was stirred for 45 min and poured into ice cold aqueous ammonium chloride solution (3 mL). The resulting mixture was then extracted with ether (4 x 5 mL). The organic extracts were dried over magnesium sulphate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave the allylic tertiary alcohol **69** (32 mg, 78% yield); ir 3500 cm$^{-1}$ (OH); $^{1}$Hmr δ5.5 (dd, 1H, J = 6 Hz, J' = 1 Hz, $-CH=\overset{|}{C}CO-$), 1.18 (s, 3H, $-\overset{|}{C}OHC\underline{H_3}$), 1.1 (s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), and 1.04 (d, 6H, J =

8 Hz, $-CH(C\underline{H}_3)_2$); ms $M^+$ 252.1722 (calcd. for $C_{15}H_{24}O_3$: 252.1726).

## (1R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-2,6-dimethylbicyclo[4.2.0]oct-2-en-4-one (**70**)

To a stirred slurry of pyridinium dichromate (552 mg, 1.47 mmol) in dichloromethane (3 mL), there was added in one protion a solution of the tertiary alcohol **63** (168 mg, 0.67 mmol) in dichloromethane (2 mL)) at room temperature. The resulting dark red-black mixture was allowed to stir for 4 h at room temperature, and was diluted with an equal volume of ether. The ethereal solution was filtered over magnesium sulfate to remove chromium impurities. The black residue was thoroughly washed with ether and also filtered over magnesium sulphate. The filtrate was concentrated and purified by column chromatography on silica gel, eluting with 5% ether in petroleum ether, to give the enone **70** (145 mg, 84% yield); ir 1665 (enone C=O) and 1620 $cm^{-1}$ (enone C=C); $^1$Hmr $\delta$ 3.90 (m, 4H, $-OCH_2CH_2O-$), 1.82 (s, 3H, $CH_3\overset{|}{C}=\overset{|}{C}CO-$), 1.22 s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), 1.09 (d, 6H, J = 3Hz, $-CH(C\underline{H}_3)_2$); ms $M^+$ 250.1560 (calcd. for $C_{15}H_{22}O_3$: 250.1569).

### 1R*,2R*,3R*,4R*,6R*)-7,7-Ethylenedioxy-3,4-epoxy-3-isopropyl-2,6-dimethylbicyclo[4.2.0]octan-2-ol (**71**)

To a stirred solution of the epoxy ketone **67** (31 mg, 0.12 mmol) in anhydrous ether (2 mL) at -78°C, was added an ethereal solution of methyllithium (0.092 mL, 1.6 M). The resulting mixture was allowed to come to room temperature, stirred for 1 h, and quenched by addition of water (1 mL). The organic layer was separated and the aqueous layer extracted with ether (3 x 5 mL). The combined organic layers were washed with water (2 x 5 mL), dried over anhydrous magnesium sulfate, filtered and concentrated. Purification by column chromatography gave the tertiary epoxy alcohol **71** (22 mg, 67% yield); ir 3530 $cm^{-1}$ (OH) and 1248 $cm^{-1}$ (epoxide): $^1$Hmr $\delta$4.9 (m, 4H, $-OCH_2CH_2O-$). 3.32 (s, 1H, -OH), 3.16 (d, 1H, J = 6 Hz, $-C\underline{H}O-$), 1.24 (s, 3H, $-\overset{|}{C}(OH)C\underline{H}_3$), 1.22 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.08 and 0.84 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 268.1676 (calcd. for $C_{15}H_{24}O_4$: 268.1675).

### (1R*,3R*,4R*,6R*)-7,7-Ethylenedioxy-3,4-epoxy-3-isopropyl-6-methyl-2-methylenebicyclo[4.2.0]octane (**72**)

To a benzene solution of the epoxy alcohol **71** (29 mg, 0.11 mmol), was added pyridine (0.088 mL) followed by thionyl chloride (0.022 mL, 0.3 mmol) under an argon atmosphere. The resulting mixture was stirred at room temperature for 2 h. It was then diluted with water and extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated to give the crude product. Column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave the vinyl epoxide **72** (7 mg, 25% yield); ir 1620 (C=C) and 1240 cm$^{-1}$ (epoxide); $^{1}$Hmr $\delta$ 5.74, 5.04 (both d, 1H each, J = 2 Hz each, $-\overset{|}{C}=CH_2$), 3.34 (d, 1H, J = 4 Hz, $-\overset{|}{C}HO-$); ms M$^{+}$ 250.1567 (calcd. for $C_{15}H_{22}O_2$: 250.1570).

### (1R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]octa-2,3-diene 73

At -78°C, to a solution of the enone **59** (293 mg, 1.24 mmol) in anhydrous ether (5 mL), was added 1.5 M methyllithium (1 mL, 1.49 mmol). After allowing the temperature of the dry-ice/acetone bath to warm up to 0°C, *p*-toluenesulfonyl isocyanate (293 mg, 1.49 mmol) was added. After stirring the solution for 1 h at 0°C, ice-cold water was added to destroy any excess isocyanate. A solution of aqueous saturated ammonium chloride was added and the resulting mixture extracted with dichloromethane. The organic extracts were washed with water, dried, filtered, and concentrated. The residue (910 mg) was pyrolyzed with the Kuhrgelrohr distillation apparatus at 110°C under reduced pressure (~0.5 torr), collecting the distillate in an ice-cold trap. The distillate was purified by column chromatography on silica gel. Elution with 5% ether in _n_-hexane gave the diene **73** (148 mg, 50% yield); ir: 1610 cm$^{-1}$ (C=C): $^1$Hmr $\delta$5.72 (br t, 1H, J = 4 Hz, $-C\underline{H}=\overset{|}{C}-\overset{|}{C}=CH_2$) 4.96, 4.86 (both s, 1H each, $-CH\overset{|}{C}-\overset{|}{C}=C\underline{H_2}$), 4.9 (m, 4H, $-OCH_2CH_2O-$) 1.10 (d, 6H, J = 8 Hz, $-CH(C\underline{H_3})_2$); ms M$^+$ 234.1621 (calcd. for $C_{15}H_{22}O_2$: 234.1621).

## 2-Hydroxyethyl (3-isopropyl-2,6-dimethylphenyl) acetate (74)

A solution of _m_-chloroperbenzoic acid (22 mg, 0.13 mmol) in dichloromethane (0.5 mL) was added to a solution of the diene **67** (21 mg, 0.09 mmol) in dichloromethane (1 mL) at 0°C under an argon atmosphere. After 30 min, a 10% aqueous sodium sulfite solution (0.5 mL) was added and the mixture was poured into a 10% aqueous sodium bicarbonate solution (2 mL). It was then extracted with dichloromethane (3 x 5 mL). The organic extracts were washed with brine, dried, and concentrated. Column chromatography on silica gel, eluting with 50% ethyl acetate in _n_-hexane, gave ester **74** (16 mg, 69% yield): ir

3600 (-OH), and 1725 $cm^{-1}$ (ester C=O); $^1$Hmr δ7.14, 7.04 (both doublet, 1H each, J = 8 Hz each, aromatic C-3H, C-4H), 4.22, 3.84 (both t, 2H each, J = 4 Hz each, $-OC\underline{H}_2C\underline{H}_2OH$), 3.24 (quintet, 1H, J = 7 Hz, $-C\underline{H}(CH_3)_2$), 2.3, 2.24 (both s, 3H each, $ArC\underline{H}_3$), and 1.23 (d, 6H, J = 7 Hz, $-CH(C\underline{H}_3)_2$); ms $M^+$ 250.1577 (calcd. for $C_{15}H_{22}O_3$: 250.1570).

## (1R*,2R*,6R*)-2-Acetoxy-7,7-ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-3-ene (**75**)

The allylic alcohol **68** (101 mg, 0.42 mmol) was dissolved in pyridine (2 mL) at 0°C under an argon atmosphere. Acetic anhydride (87 mg, 0.85 mmol) was added and the mixture was allowed to warm up to room temperature. It was stirred at this temperature for 8 h and poured into ice cold 2 N hydrochloride acid. The resulting mixture was extracted with dichloromethane. The combined extracts were washed with brine solution, dried, filtered, and concentrated to give the allylic acetate **75** (66 mg, 56% yield); ir 1735 $cm^{-1}$ (ester C=O); $^1$Hmr δ5.66 (br t, 1H, J = 4 Hz, $-\overset{|}{C}HOCO-$) 5.5 (m, 1H, $-CH=\overset{|}{C}-$), 4.9 (m, 4H, $-OCH_2CH_2O-$), 2.08 (s, 3H, $-OCOCH_3$), 1.14 (s, 3H, $-\underset{|}{\overset{|}{C}}CH_3$), 1.02 and 0.94 (both d, 3H each, J = 8 Hz each,

-CH(C$\underline{H}_3$)$_2$); ms M$^+$ 280.1673 (calcd. for $C_{16}H_{24}O_4$: 280.1675).

### (1R*,2R*,3*R,4R*,6R*)-2-Acetoxy-3,4-epoxy-7,7-ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]octane (**76**)

To a solution of the allylic acetate **75** (49 mg, 0.18 mmol) in dichloromethane (2 mL) at 0°C under an argon atmosphere, was added a solution of m-chloroperbenzoic acid (36.7 mg, 0.26 mmol) in dichloromethane (0.5 mL). After 1 h, a 10% aqueous sodium sulfite solution (1 mL) was added and the mixture was poured into a 10% aqueous sodium bicarbonate solution (2 mL). It was extracted with dichloromethane (4 x 5 mL). The combined organic extracts were washed with brine, dried, and concentrated. Column chromatography on silica gel, eluting with 10% ethyl acetate in n-hexane, gave the epoxy acetate **76** (38 mg, 72% yield): ir 1737 (acetate C=O) and 1241 cm$^{-1}$ (epoxide); $^1$Hmr $\delta$5.48 (d, 1H, J = 6 Hz, $-\overset{|}{C}HOCO-$), 4.82 (m, 4H, $-OCH_2CH_2O-$), 3.15 (d, 1H, J = 4 Hz, $-\overset{|}{C}HO-$), 2.12 (s, 3H, $-OCOCH_3$), 1.20 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 0.92 and 0.82 (both d, 3H each, J = 8 Hz each, -CH(C$\underline{H}_3$)$_2$); ms m/e 253.1443 (M$^+$-43; calcd. for $C_{14}H_{21}O_4$: 253.1440).

### (1R*,2R*,6R*)-2-Acetoxy-7,7-ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]octane-3,4-diol (77)

The epoxy acetate **76** (38 mg, 0.13 mmol) was dissolved in benzene (1 mL) at 0°C. Boron trifluoride etherate (0.08 mL, 0.67 mmol) was then added via syringe. The resulting mixture was stirred at 0°C for 1 h. To the reaction mixture was added saturated aqueous sodium bicarbonate and the resulting mixture was extracted with ether (4 x 5 mL). The ether extracts were washed with brine solution, dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the residue gave the diol **77** (41 mg, 100% yield): ir 3460 (O-H) and 1734 $cm^{-1}$ (acetate C=O); $^1$Hmr $\delta$ 5.18 (d, 1H, J = 6 Hz, $-\overset{|}{C}HOCO-$), 4.12 (br t, 1H, J = 4 Hz, $-\overset{|}{C}\underline{H}OH$), 2.0 (s, 3H, $-OCOCH_3$), 1.18 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), and 0.89 (d, 6H, J = 8 Hz, $-CH(\underline{CH_3})_2$); ms m/e 255.1594 (calcd. for $C_{14}H_{23}O_4$: 255.1597).

### (1R*,2R*,6R*)-2-Acetoxy-7,7-ethylenedioxy-3-hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-4-one (78)

To a slurry of pyridinium dichromate (76 mg, 0.20 mmol) in dichloromethane (1 mL), was added a solution of the diol **77** (41 mg, 0.14 mmol) in dichloromethane (1 mL) at room temperature. The mixture was stirred at room temperature for 4 h. It was diluted with ether, filtered over magnesium sulfate, and concentrated. Column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave the keto alcohol **78** (34 mg, 83% yield): ir 3480 (OH), 1735 (acetate C=O) and 1710 cm$^{-1}$ (ketone C=O); $^1$Hmr $\delta$ 5.46 (d, 1H, J = 6 Hz, $-\overset{|}{\mathrm{C}}\mathrm{H}-\mathrm{OCO}-$) 2.06 (s, 3H, $-\mathrm{OCOCH_3}$), 1.4 (s, 3H, $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{CH_3}$), and 1.04, 0.74 (both d, 3H each, J = 8 Hz each, $-\mathrm{CH(C\underline{H}_3)_2}$); ms m/e 253.1429 (calcd. for $\mathrm{C_{14}H_{21}O_4}$: 253.1440).

### (1R*,2R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-2-methoxy-6-methylbicyclo[4.2.0]oct-3-ene (**79**)

Sodium hydride (80% dispersion in oil, 0.66 g) in a 50 mL round bottomed flask was freed of mineral oil by washing with distilled petroleum ether (4 x 10 mL). It was then suspended in 1,2-dimethoxyethane (10 mL) and cooled to 0°C. A solution of allylic alcohol **68** (1.3 g 5.5 mmol) in 1,2-dimethoxyethane was added dropwise to the cooled suspension. After stirring the mixture under an argon atmosphere for 30 min, methyl iodide (1.63 g, 8.2 mmol) was added. The resulting solution was stirred overnight at room temperature. The reaction mixture was poured into ice-cold water and extracted with dichloromethane (4 x 50 mL). The extracts were washed successively with water and brine solution, dried over magnesium sulfate, and concentrated. Column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave the pure product **79** (1.11, 81% yield): ir 1098 (C-O-C) $cm^{-1}$; $^1$Hmr $\delta$5.55 (br s, 1H, $-\overset{|}{C}=CH-$), 3.88 (m, 5H, $-OC\underline{H_2}C\underline{H_2}O-$ and $-\overset{|}{C}\underline{H}-OCH_3$), 3.36 (s, 3H, $-\overset{|}{C}H-OC\underline{H_3}$), 2.26 (quintet, 1H, J = 7 Hz, $-C\underline{H}(CH_3)_2$), 1.1 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.08 and 1.0 (both d, 3H each, J = 7 Hz each, $-CH(\underline{CH_3})_2$); ms m/e 252.1713 (calcd. for $C_{15}H_{24}O_3$: 252.1726). Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.40; H, 9.59; found: C, 71.10; H, 9.62.

## (1R*,2R*,3R*,4S*,6R*)- and (1R*,2R*,3S*,4R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-2-methoxy-6-methylbicyclo[4.2.0]octan-4-ol (**80**)

A dry, argon-flushed, 25 mL flask was charged with a tetrahydrofuran (5 mL) solution of the allylic ether **79** (192 mg, 0.75 mmol). A 1 M tetrahydrofuran solution of diborane (1.12 mL) was then added via syringe. The solution was stirred at room temperature for 1 h. The flask was immersed in an ice bath and water was added to destroy the excess diborane. The intermediate organoboranes were oxidized by adding, successively sodium hydroxide (3 M, 0.1 mL) and hydrogen peroxide (30%, 0.1

mL). Complete oxidation was ensured by maintaining the reaction mixture at 50°C for 1 h. The solution was poured into water and the alcohols formed were extracted with ether (3 x 20 mL). The combined extracts were washed with saturated sodium bicarbonate solution, the ether layer separated, dried over magnesium sulfate, filtered and concentrated to give a 3:1 ($^1$Hmr analysis) ratio of a mixture of crude products. Column chromatography on silica gel, eluting with 20% ethyl acetate in petroleum ether gave the major diastereomer of **80** (104 mg, 51% yield): ir 3500 (O-H) and 1100 cm$^{-1}$ (C-O-C); $^1$Hmr $\delta$3.48 (dd, 1H, J = 6 Hz, J' = 2 Hz, $-\overset{|}{C}\underline{H}OCH_3$), 3.2 (s, 3H, $-\overset{|}{C}HOC\underline{H_3}$), 2.48 (dd, 1H, J = 12 Hz, J' = 9 Hz, C-8H), $\delta$2.8 (dd, 1H, J = 12 Hz, J' = 9 Hz, C-8H), 1.96 (m, 1H, $-C\underline{H}(CH_3)_2$), 1.17 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.07 and 0.98 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H_3})_2$); ms M$^+$ 270.1831 (calcd. for $C_{15}H_{26}O_4$: 270.1832).

Further elution gave a mixture of diastereomers (28 mg, 14% yield) followed by the minor diastereomer (22 mg, 11% yield): ir 3480 (O-H) and 1099 cm$^{-1}$ (C-O-C); $^1$Hmr $\delta$3.64 (br d, 1H, J = 6 Hz, $-\overset{|}{C}\underline{H}OCH_3$), 3.26 (s, 3H, $-\overset{|}{C}HOC\underline{H_3}$), 1.22 (s, 3H, $-C\underline{H_3}$), 1.06 and 0.94 (both d, 3H each, J = 7 Hz, $-CH(C\underline{H_3})_2$; ms m/e 255.1604 (M$^+$-15) (calcd. for $C_{14}H_{23}O_4$: 255.1597).

## (1R*,2R*,3S*,6R*)-7,7-Ethylenedioxy-3-isopropyl-2-methoxy-6-methylbicyclo[4.2.0]octan-4-one (**81**)

To a mixture of alcohols **80** (118 mg, 0.44 mmol) in dichloromethane (2 mL), was added pyridinium dichromate (246 mg, 0.66 mmol). The resulting mixture was stirred at room temperature for 8 h. It was then diluted with ether (10 mL), filtered over magnesium sulfate, and concentrated. Flash column chromatography of the residue on silica gel, eluting with 10% ethyl acetate in petroleum ether, gave pure ketone **81** (105 mg, 90% yield): ir 1710 (ketone C=O) and 1190 $cm^{-1}$ (C-O-C); $^1$Hmr $\delta$ 3.76 (dd, 1H, J = 6.5 Hz, J' = 2.5 Hz, $-\overset{|}{\text{C}}\underline{\text{H}}\text{OCH}_3$), 3.28 (s, 3H, $-\overset{|}{\text{C}}\text{OC}\underline{\text{H}_3}$), 3.02 (d, 1H, J = 17 Hz, C-5H), 2.66 (dd, 1H, J = 12.5 Hz, J' = 9 Hz, C-8H), 2.1 (d, 1H, J = 17 Hz, C-5H), 1.12 (s, 3H, $-\overset{|}{\underset{|}{\text{C}}}\text{CH}_3$), and 1.04, 0.96 (both d, 3H each, J = 7 Hz each, $-\text{CH}(\text{C}\underline{\text{H}_3})_2$); ms m/e 268.1675 (calcd. for $C_{15}H_{24}O_4$: 268.1675). Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.12; H, 9.02. Found: C, 66.95; H, 8.96.

## (1R*,6R*)-7,7-Ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]oct-2-en-4-one (**82**)

Methoxy ketone **81** (120 mg, 0.45 mmol) was dissolved in benzene (2 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3 mL) was added. The resulting mixture was refluxed under an argon atmosphere for 4 h. It was then cooled to room temperature, acidified with ice cold 2 M hydrochloride acid, extracted with dichloromethane (4 x 20 mL), washed with a brine solution, dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether to give pure enone **82** (98 mg, 91% yield): ir 1778 (enone C=O) and 1615 $cm^{-1}$ (C=C); $^1$Hmr $\delta$ 6.45 (d, 1H, J = 5 Hz, $-\underline{CH}=\overset{|}{C}CO-$), 3.87 (m, 4H, $-OCH_2CH_2O-$), 2.96 (septet, 1H, J = 7 Hz, $-\underline{CH}(CH_3)_2$), 2.82 (dd, J = 12 Hz, J' = 10 Hz, C-8H), 2.56 (d, 1H, J = 16 Hz, C-5H), 2.46 (quintet, 1H, J = 10 Hz, J' = J" = 5 Hz, $-\overset{|}{C}\underline{H}-$), 2.16 (d, 1H, J = 16 Hz, C-5H), 2.08 (dd, 1H, J = 12 Hz, J' = 5 Hz, C-8H), 1.24 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.06 and 1.0 (both d, 3H each, J = 7 Hz each, $-CH(\underline{CH_3})_2$); ms $M^+$ 236.1416 (calcd. for $C_{14}H_{20}O_3$: 236.1413). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.14; H, 8.53. Found: C, 70.91; H, 8.47.

### (1R*,2S*,3R*,6R*)- and (1R*,2R*,3S*,6R*)-7,7-Ethylenedioxy-3-isopropyl-6-methyl-2-vinylbicyclo[4.2.0]octan-4-one (**83**)

A suspension of cuprous iodide (0.021 g, 0.11 mmol) in tetrahydrofuran (5 mL) was cooled to 0°C under an argon atmosphere. A solution of 1.3 M vinylmagnesium bromide in tetrahydrofuran (2 mL, 2.6 mmol) was added via a syringe and the mixture was cooled to -25°C. After 15 min at this temperature, a solution of enone **82** (101 mg, 0.42 mmol) in tetrahydrofuran (5 mL) was added. After 20 min the mixture was added to an ice-cold solution of aqueous 2 M hydrochloric acid (10 mL) with stirring. It was then extracted with dichloromethane (3 x 20 mL). The combined organic extract was dried, filtered, and concentrated. The crude material was purified on a silica gel column, eluting with 5% ethyl acetate in petroleum ether, to give the vinyl ketone **83** (93 mg, 85% yield): ir 1705 (ketone C=O) and 1640 (C=C) $cm^{-1}$; $^1$Hmr $\delta$ 5.4 (ddd, 1H, J = 17 Hz, J' = J" = 9 Hz, $-C\underline{H}=CH_2$), 5.1 (dd, 1H, J = 17 Hz, J' = 2.5 Hz, $-CH=C\underline{H}H$), 5.08 (dd, J = 9 Hz, J' = 2.5 Hz, $-CH=CH\underline{H}$), 3.9 (m, 4H, $-OCH_2CH_2O-$), 3.1 (d, 1H, J = 12 Hz, C-5H), 1.8 (d, 1H, J = 12 Hz, C-5H), 1.1 (s, 1H, $-\overset{|}{\underset{|}{C}}CH_3$), and 1.08, 0.92 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 264.1710 (calcd. for $C_{16}H_{24}O_3$: 264.1730).

### (1R*,2S*,3R*,6R*)- (**85**) and (1R*,2R*,3S*,6R*)-2-Carbomethoxy-7,7-ethylenedioxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-4-one (**86**)

Ruthenium dioxide (71 mg) was suspended in acetone

(25 mL) and a solution of sodium metaperiodate (710 mg) in water (10 mL) was added. The mixture was stirred at room temperature until a clear yellow solution was obtained. Solid sodium metaperiodate (1.0 g) was introduced and a solution of vinyl ketone 83 (604 mg, 2.3 mmol) in acetone (10 mL) was then added dropwise with stirring. The reaction mixture was stirred for 4 h and isopropyl alcohol (10 mL) was added. After 30 min, the mixture was filtered and the residue thoroughly washed with acetone. Most of the solvent was evaporated and the aqueous solution made basic with 1 N aqueous potassium hydroxide solution. The solution was washed with ethyl acetate (3 x 30 mL) and the aqueous fraction acidified with 1 N aqueous hydrochloric acid solution. Extraction with dichloromethane (3 x 30 mL) was followed by drying of the dichloromethane extracts. Filtration and concentration gave the crude acid (622 mg) which was dissolved in acetone (10 mL). Potassium carbonate (622 mg) was added and the mixture was stirred for 30 min. Methyl iodide (0.48 mL) was added and the mixture was stirred overnight. The resulting mixture was poured into ice cold dilute aqueous hydrochloric acid and extracted with dichloromethane (5 x 20 mL). The dichloromethane extract was dried, filtered and concentrated. Column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether afforded

keto ester (**85**) (332 mg, 49% yield): ir 1735 (ester C=O) and 1710 cm$^{-1}$ (ketone C=O); $^{1}$Hmr $\delta$ 3.86 (m, 4H, $-OCH_2CH_2O-$), 3.7 (s, 3H, $-OCH_3$), 3.09 (dd, J = J' = 12 Hz, C-2H), 3.02 (d, 1H, J = 15 Hz, C-5H), 2.66 (dd, 1H, J = 13.5 Hz, J' = 9 Hz, C-8H), 2.3 (dd, 1H, J = 12 Hz, J' = 3.5 Hz, C-3H), 2.2 (dd, 1H, J = 13.5 Hz, J' = 3 Hz, C-8H), 1.96 (d of septet, 1H, J = 7 Hz, J' = 3.5 Hz, $-C\underline{H}(CH_3)_2$), 1.84 (d, 1H, J = 13 Hz, C-5H), 1.76 (ddd, 1H, J = 12 Hz, J' = 9 Hz, J" = 3 Hz, C-1H), 1.14 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.06 and 0.91 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H_3})_2$); ms M$^{+}$ 296.1621 (calcd. for $C_{16}H_{24}O_5$: 296.1624).

Further elution gave the other diastereoisomer **86** (140 mg, 21% yield): ir 1740 (ester C=O) and 1700 cm$^{-1}$ (ketone C=O); $^{1}$Hmr $\delta$ 4.04 (dd, 1H, J = 11.5 Hz, J' = 4 Hz, C-2H), 3.94 (s, 3H, $-OCH_3$), 3.86 (m, 4H, $-OCH_2CH_2O-$), 2.94 (ddd, 1H, J = 11.5 Hz, J' = 4 Hz, J" = 1Hz, C-3H), 2.57 (dd, 1H, J = 15 Hz, J' = 1 Hz, C-5H), 2.36 (ddd, 1H, J = J' = 9 Hz, J" = 4 Hz, $-\overset{|}{\underset{|}{C}}H$), 2.16 (d, 2H, J = 9 Hz, C-8H), 2.12 (d, 1H, J = 15 Hz, C-5H), 1.94 (d of septet, 1H, J = 7 Hz, J' = 4 Hz, $-C\underline{H}(CH_3)_2$), 1.24 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.0, and 0.82 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H_3})_2$); ms M$^{+}$ 296.1619 (calcd. for $C_{16}H_{24}O_5$: 296.1624). Anal. Calcd. for $C_{16}H_{24}O_5$: C, 64.8; H, 8.17. Found: C, 65.16; H, 8.26.

### (1R*,2R*,3S*,6R*)-2-Carbomethoxy-3-isopropyl-6-methylbicyclo[4.2.0]octa-4,7-dione (**87**)

To a stirred solution of the keto ester **86** (202 mg, 0.68 mmol) in acetone (5 mL), was added a solution of *p*-toluenesulfonic acid (0.16 g) in water (0.5 mL) at room temperature. The resulting mixture was refluxed overnight. The reaction mixture was cooled to room temperature and poured into ether (20 mL). The organic layer was washed successively with water, saturated sodium bicarbonate solution, water and saturated brine solution. The ether layer was dried over magnesium sulfate and concentrated. Column chromatography on silica gel, eluting with 30% ethyl acetate in petroleum ether, gave the cyclobutanone **87** (124 mg, 72% yield): ir 1781 (four membered C=O), 1734 (ester C=O) and 1714 $cm^{-1}$ (six membered C=O); $^1$Hmr $\delta$ 3.68 (s, 3H, $-O-CH_3$), 3.22 (dd, 1H, J = 4 Hz, J' = 2.5 Hz, C-2H), 2.86 (dd, 1H, J = 18 Hz, J' = 4 Hz, C-8H), 2.76 (d, 1H, J = 18.5 Hz, C-5H), 2.68 (ddd, 1H, J = 10 Hz, J' = 4 Hz, J" = 2.5 Hz, $-\overset{|}{\underset{|}{C}}H$), 2.46 (d, 1H, J = 18.5 Hz, C-5H), 2.26 (septet, 1H, J = 7.5 Hz, $-C\underline{H}(CH_3)_2$), 1.32 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.00 and 0.86 (both d, 3H each, J = 7.5 Hz each, $-CH(C\underline{H_3})_2$); ms $M^+$ 252.1357 (calcd. for $C_{14}H_{20}O_4$: 252.1362).

## (1R*,2R*,3S*,6R*,7R*)-2-Carbomethoxy-7-hydroxy-3-isopropyl-6-methyl-7-vinylbicyclo[4.2.0]octan-4-one (**88**)

To a tetrahydrofuran (5 mL) solution of the diketo ester **87** (234 mg, 0.9 mmol) at -78°C was added 1.05 M vinyllithium (1.06 mL, 1.1 mmol) under an argon atmosphere. The reaction mixture was stirred for 1 h at -78°C. Aqueous ammonium chloride solution was added to the reaction mixture and the resulting mixture extracted with ether (4 x 10 mL). The combined ether extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated. Column chromatography on silica gel, eluting with 40% ethyl acetate in petroleum ether, gave the keto alcohol **88** (220 mg, 85% yield): ir 3444 (O-H), 1735 (ester C=O) and 1709 (six-membered C=O); $^1$Hmr $\delta$ 6.02 (dd, 1H, J = 17 Hz, J' = 11 Hz, $CH_2=C\underline{H}-$), 5.46 (dd, 1H, J = 17 Hz, J' = 1 Hz, $C\underline{H}H=CH-$), 5.34 (dd, 1H, J = 11 Hz, J' = 1 Hz, $CH\underline{H}=CH-$), 2.58 (d, 1H, J = 18 Hz, C-5H), 2.0 (d, 1H, J = 18 Hz, C-5H), 1.14 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 0.98 and 0.8 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H}_3)_2$); ms m/e 280.1660 (calcd. $C_{16}H_{24}O_4$: 280.1675).

## (1R*,2R*,3S*,6R*,7R*)-2-Carbomethoxy-7-(epoxyethyl)-7-hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]octan-4-one (**89**)

A solution of _m_-chloroperbenzoic acid (80% purity, 162 mg, 0.94 mmol) in dichloromethane (2 mL) was added dropwise to a solution of vinyl alcohol **88** (175 mg, 0.63 mmol) in dichloromethane (2 mL) at 0°C. After the addition the mixture was stirred for 4 h at room temperature under an argon atmosphere. A 10% aqueous sodium sulfite solution (2 mL) was added and the mixture was poured into a 10% aqueous sodium bicarbonate solution (10 mL). The organic fraction was separated, washed with brine, dried and concentrated. The crude material was purified on a silica gel column, eluting with 50% ethyl acetate in hexane, to give one diastereomer of epoxy alcohol **89** (82 mg, 44.3% yield); ir 3461 (O-H), 1734 (ester C=O) and 1711 cm$^{-1}$ (ketone C=O); $^1$Hmr $\delta$3.72 (s, 3H, -O-CH$_3$), 3.06 (dd, 1H, J = 4 Hz, J' = 2.5 Hz, -C$\underline{H}$HO-), 2.96 (d, 1H, J = 12 Hz, C-5H), 2.88 (t, 1H, J = 4 Hz, -$\overset{|}{\text{C}}$HO-), 2.68 (dd, 1H, J = 4 Hz, J' = 2.5 Hz, -CH$\underline{H}$O-), 1.16 (s, 3H, -$\overset{|}{\underset{|}{\text{C}}}$CH$_3$), 1.06 and 0.9 (both d, 3H each, J = 7 Hz each, -CH(C$\underline{H}_3$)$_2$); ms M$^+$ 296.1624 (calcd. for $C_{16}H_{24}O_5$: 296.1624).

Further elution gave a mixture of epoxides **89** (53 mg, 29% yield). Continued elution gave the second epoxide (46 mg, 25% yield): ir 3473 (O-H), 1734 (ester C=O), 1711 (ketone C=O) and 1245 cm$^{-1}$ (epoxide); $^1$Hmr $\delta$3.72 (s, 3H, -O-CH$_3$), 3.36 (dd, 1H, J = 4 Hz, J' = 2.5 Hz, -$\overset{|}{\text{C}}$HO-), 1.16 (s, 3H, -$\overset{|}{\underset{|}{\text{C}}}$-C$\underline{H}_3$), 1.06 and 0.90 (both d, 3H each, J = 7 Hz each, $-CH(C\underline{H}_3)_2$); ms $M^+$ 296.1626 (calcd. for $C_{16}H_{24}O_5$: 296.1624).

### (1S,2R,4R*,7R*,8R*)-8-Carbomethoxy-2-hydroxymethyl-7-isopropyl-4-methyl-6-oxo-1-oxaspiro[2.7.$0^{4,9}$]decane (**92**)

To a solution of the epoxy alcohol **89** (25 mg, 0.08 mmol) in dichloromethane (2 mL) at 0°C, was added stannic chloride (0.018 mL, 0.16 mmol) with stirring under an argon atmosphere. After 10 min, saturated aqueous sodium bicarbonate solution was added to the reaction mixture. The resulting solution was then extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered, and concentrated. Column chromatography of the resulting residue on silica gel, eluting with 50% ethyl acetate in petroleum ether gave the epoxy alcohol **92** (24 mg, 96% yield): ir 3430 (-OH), 1735 (ester C=O), and 1714 $cm^{-1}$ (ketone C=O); $^1$Hmr $\delta$ 3.72 (s, 3H, $-OCH_3$), 1.14 (s, 3H, $-\overset{|}{\underset{|}{C}}H_3$), 1.04, and 0.84 (both d, 3H each, J = 8 Hz each, $-CH(CH_3)_2$); ms $M^+$ 296.1628 (calcd. for $C_{16}H_{24}O_5$: 296.1658).

## (1R*,2R*,3R*,6R*,7S*)-7-(1,2-dibromoethyl)-2-carbomethoxy-7-hydroxy-3-isopropyl-6-methylbicyclo[4.2.0]-octan-3-one (**94**)

The vinyl alcohol **88** (29 mg, 0.1 mmol) in carbon tetrachloride at 0°C was titrated with bromine (0.017 mL, 0.12 mmol) under an argon atmosphere. The resulting mixture was extracted with dichloromethane (3 x 10 mL), washed with saturated aqueous sodium bicarbonate, and water. The organic layer was then dried with sodium sulphate, filtered and concentrated. The resulting residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum, to give the dibromide **94** (41 mg, 91% yield): ir 3520 (O-H), 1732 (ester C=O) and 1712 cm$^{-1}$ (ketone C=O); $^1$Hmr δ3.72 (s, 3H, $-OCH_3$), 1.22 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.04, and 0.88 (both d, 3H and each, J = 8 Hz each, $-CH(C\underline{H_3})_2$): ms m/e 358.0815 and 360.0721 (M$^+$-80; calcd. for $C_{16}H_{23}O_4Br$: 358.0813 and 360.0727).

## (1S*,2R*,4R*,7R*,8R*)-2-Bromomethyl-8-carbomethoxy-7-isopropyl-4-methyl-6-oxo-1-oxaspiro[2.7.0$^{4,9}$]decane (**96**)

A solution of the dibromide **94** (35 mg, 0.08 mmol) in pyridine (2 mL) was heated to reflux overnight under an argon atmosphere. The reaction mixture was cooled to room temperature, acidified with ice cold 1 N hydrochloric acid, and extracted with dichloromethane (4 x 5 mL). The combined dichloromethane extracts were dried over sodium sulphate, filtered, and concentrated. Column chromatography of the residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave **96** (23 mg, 82% yield): ir 1733 (ester C=O) and 1711 $cm^{-1}$ (ketone C=O); $^1$Hmr δ 3.74 (s, 3H, $-OCH_3$), 1.24 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.06, and 0.96 (both d, 3H each, J = 8 Hz each, $-CH(C\underline{H}_3)_2$); ms m/e 278.1511 ($M^+$-80) (calcd. for $C_{16}H_{22}O_4$: 278.1549).

### (1S,2R*,4R*,7R*,8R*)-2-Acetoxymethyl-8-carbomethoxy-7-isopropyl-4-methyl-6-oxo-1-oxaspiro[2.7.0$^{4,9}$]decane (**93**)

The epoxy alcohol **92** (19 mg, 0.06 mmol) was dissolved in pyridine (1 mL) at 0°C and acetic anhydride (0.01 mL, 0.13 mmol) and the resulting solution was stirred, under an argon atmosphere, for 4 h at room temperature. Saturated aqueous sodium bicarbonate was added to the reaction mixture and extracted with ether (3 x 10 mL). The combined ether extracts were dried over magnesium sulfate, filtered, and concentrated to give the crude product. Column chromatography of the crude product on silica gel eluting with 30% ethyl acetate in petroleum ether gave **93** (18 mg, 82% yield): ir 1735 (acetate C=O) and 1713 cm$^{-1}$ (ketone C=O); $^1$Hmr $\delta$ 3.70 (s, 3H, $-OCH_3$), 2.12 (s, 3H, $-OCOCH_3$), 1.08 (s, 3H, $-\overset{|}{\underset{|}{C}}CH_3$), 1.04, and 0.88 (both d, 3H each, J = 8 Hz each, $-CH(CH_3)_2$); ms M$^+$ 338.1742 (calcd. for $C_{18}H_{26}O_6$: 338.1730).

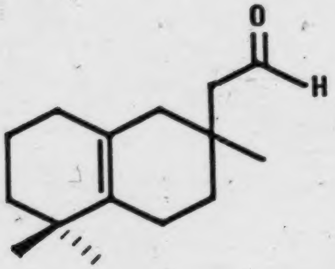
# CHAPTER II

# SYNTHETIC STUDIES ON ISOACANTHODORAL

# INTRODUCTION

In 1984, Andersen et al.[93] reported the isolation of three sesquiterpenes bearing an aldehyde function from the extracts of the nudibranch Acanthodoris nanaimoensis collected in Barkley Sound, British Columbia. Nanaimoal, the major component, was assigned the structure **1** based on its spectral data, the biogenetic isoprene rule and an unambiguous synthesis of its p-bromophenylurethane derivative. The structures of the minor components,[94] acanthodoral (**2**) and isoacanthodoral (**3**) were resolved by single crystal X-ray diffraction analysis of the p-bromophenylurethane and the dinitrophenylhydrazone derivatives respectively. The novel sesquiterpenoid skeletons of nanaimoal (**1**), acanthodoral (**2**), and isoacanthodoral (**3**) were given the names nanaimoane, acanthodorane, and isoacanthodorane respectively.

The biogenesis of these sesquiterpenes[94] was proposed, in which farnesyl pyrophosphate (**4**) first cyclizes (Scheme I) to an intermediate **5**. This is further transformed to the aldehyde **2** by a 2 + 2 addition reaction, hydrolysis and oxidation. Loss of Ha (path a) in **2** will give **1**, while the loss of Hb (path b) yields **3**.



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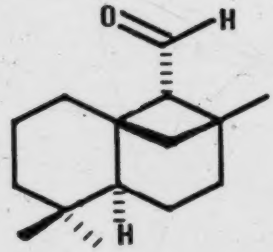

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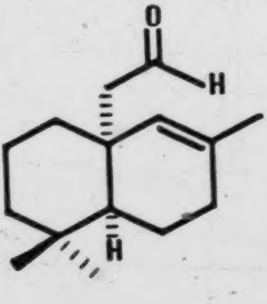
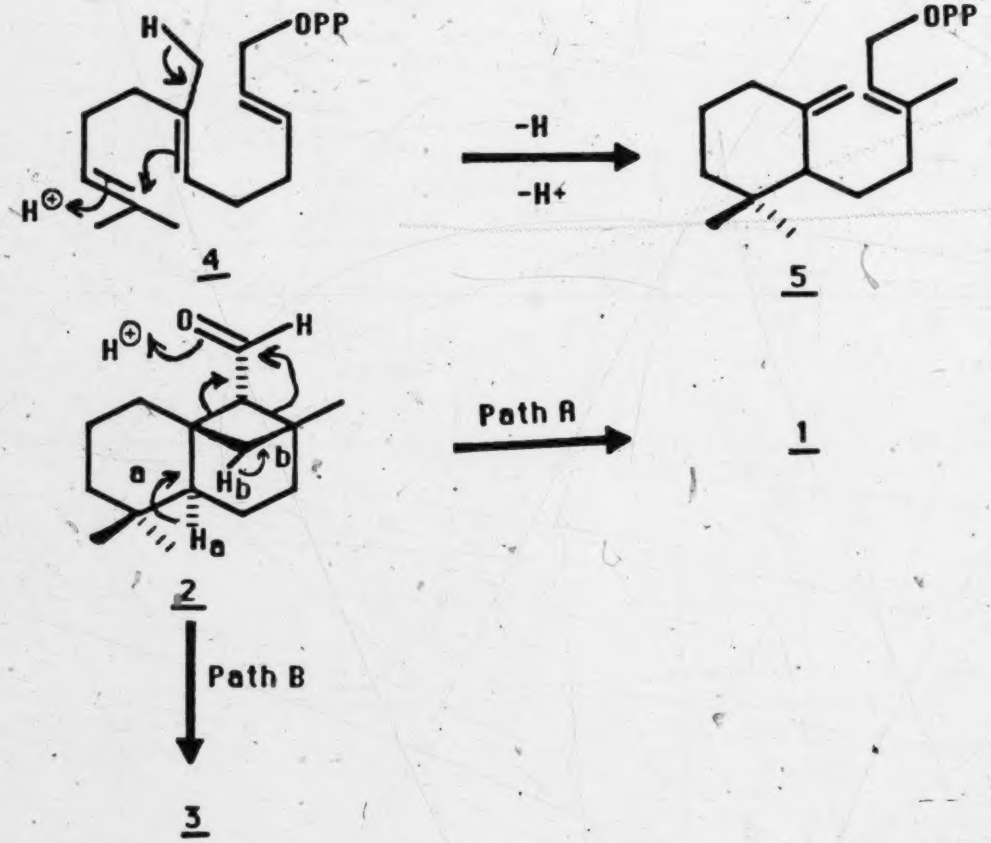
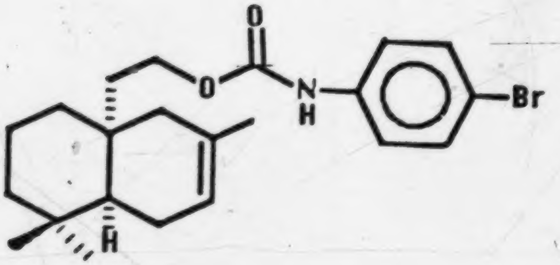


3

# SCHEME 1





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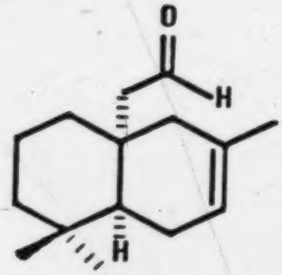

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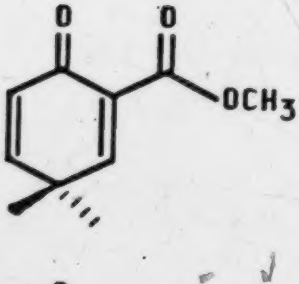


8

During the course of their studies,[95] it was observed that the *p*-bromophenylurethane derivative of the corresponding alcohol, obtained by the reduction of isoacanthodoral **2**, was converted quantitatively to the isomeric compound **6** upon treatment with 98-100% formic acid. The aldehyde **7**, corresponding to **6**, was also suspected to be a natural product.[96]

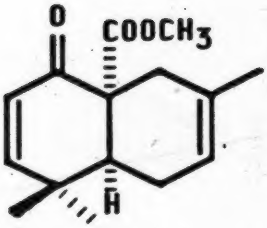
Several years ago, a synthetic scheme was designed in our laboratory which involved compound **10** as the key intermediate in the synthesis of α- and β-himachalene. During that study the adduct **9** was observed as the major product in the Diels Alder reaction between 2-carbomethoxy-4,4-dimethylcyclohexadien-1-one (**8**) and isoprene in the presence of boron trifluoride etherate. Interestingly, the production of the adduct **9** as the major product violated the "*para*" rule. Compound **9** possessed the basic carbon framework of isoacanthodoral (**2**) and therefore offered itself as an attractive intermediate for the synthesis of the isoacanthodorane skeleton. After reduction of compound **9** to the saturated ketone followed by conversion of the ketone functionality to a methylene group, a reduction of the ester to an aldehyde and a one carbon homologation would give compound **7**. Efforts made towards the synthesis of the aldehyde **7** are outlined in this chapter of the thesis.

# RESULTS AND DISCUSSION

Diels-Alder reaction between 2-carbomethoxy-4,4-dimethyl-2,5-cyclohexadien-1-one (**8**) and isoprene in the presence of boron trifluoride etherate gave a mixture of two 1:1 adducts in the ratio of 70:30 ($^1$Hmr analysis). The major product **9** displayed the same spectral characteristics as reported,[97] and so did the minor product **10**. As mentioned earlier on, the major product **9** was used as the key intermediate for the synthetic studies on the isoacanthodrane skeleton.

With compound **9** in hand, we set out to first reduce the double bond of the enone moiety to the saturated ketone, which would eventually be converted to a methylene unit. Hydrosilanes, in the presence of tris-triphenylphosphine rhodium(I) chloride, have been shown[98] to give silyl enol ethers which readily undergo hydrolysis[99] to give saturated ketones. This was the approach used to convert the enone **9** to the saturated ketone **11**, since the other methods[24,100] would also effect reduction of the ester functionality or the isolated double bond.

Thus, finely divided solid enone **9** suspended in triethylsilane in the presence of Wilkinson's catalyst was converted to **12** within 24 h. The pure product was



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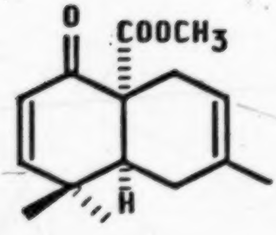

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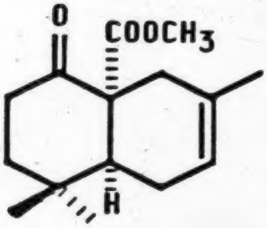

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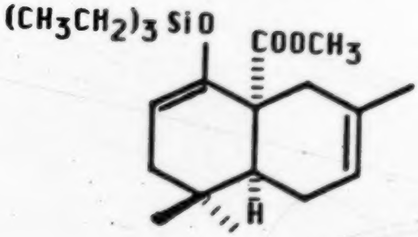

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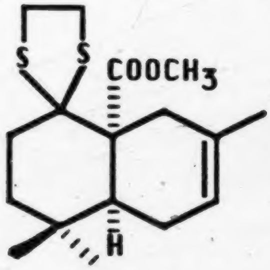

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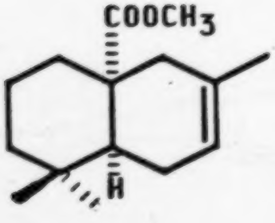

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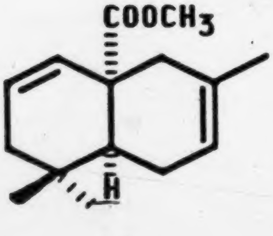

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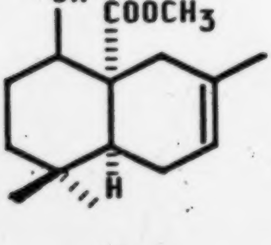


16

obtained in 96% yield. The silyl enol ether **12** was hydrolyzed with potassium carbonate in aqueous methanol to give the saturated ketone **11** in 90% yield. The ir spectrum displayed bands at 1743 and 1712 $cm^{-1}$ due to the saturated ester and ketone respectively. The $^1$Hmr spectrum showed a multiplet at $\delta$5.40 due to the vinyl proton and the methyl groups appeared as singlets at $\delta$3.72 (ester), 1.65 (vinylic), 1.00, and 0.90. The compound also showed a molecular ion peak at m/e 250.1567 in the mass spectrum indicative of the chemical formula $C_{15}H_{22}O_3$.

As mentioned earlier, the saturated ketone had to be converted to a methylene unit. The direct methods for this operation either involve strongly acidic[101] (Clemensen) or basic conditions[102] (Wolff-Kishner) both of which could effect decarbomethoxylation of the ester moiety in compound **11** since it is $\beta$ to the ketone. To circumvent this situation, other methods had to be used.[103-107]

Thioketals are known to be converted to their corresponding hydrocarbons upon exposure to Raney nickel. Since the conditions under which the thioketals are formed would also leave the ester intact, this was the approach that was tried first. Thus the keto ester **11** was treated with 1,2-ethanedithiol in the presence of boron trifluoride etherate to give the thioketal **13** in 91%

yield. The ir spectrum displayed a band at 1740 $cm^{-1}$ due to an ester. The $^1$Hmr spectrum showed a vinyl multiplet at $\delta$5.26. A singlet at $\delta$3.66 confirmed the presence of the ester function and the singlet at $\delta$1.62 was attributed to the vinylic methyl group. Two other methyl singlets appeared at $\delta$0.96 and 0.84. The mass spectrum showed a molecular ion peak at m/e 326.1369 indicating the molecular formula $C_{17}H_{26}O_2S_2$.

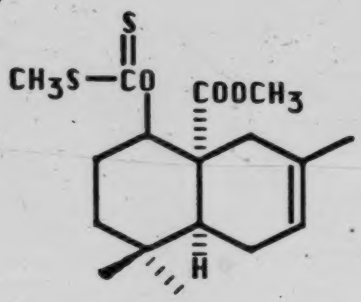
Raney Nickel reduction[104] of **13** gave a 1:1 mixture of products in 87% yield. One of the products displayed a band at 1729 $cm^{-1}$ in the ir spectrum due to an ester. The $^1$Hmr spectrum showed a multiplet at $\delta$5.26 due to a vinyl proton. The vinylic methyl group appeared as a broad singlet at $\delta$1.62, while the other two methyl groups appeared as singlets at $\delta$0.94 and 0.82. The mass spectrum showed a molecular ion peak at m/e 236.1768 for the chemical formula $C_{15}H_{24}O_2$. The spectral data suggested that the compound was the desired ester **14**. The other product showed a band at 1730 $cm^{-1}$ due to an ester in the ir spectrum. The $^1$Hmr spectrum exhibited three vinylic protons at $\delta$5.66, 5.60, and 5.36. The mass spectrum showed a molecular ion peak at m/e 234.1614 for the chemical formula $C_{15}H_{22}O_2$. These spectral data suggest the structure **15**.

Due to the low yield of the required ester **14** and the production of the diene **15**, an alternative route[105-107] to the ester **14** was explored. Barton[105] and others[14] have demonstrated that, on reaction with tri-_n_-butylstannane, _S_-alkyl xanthates, derived from the corresponding alcohols, yield the corresponding hydrocarbons. The related derivatives such as thionobenzoate,[105,107] thiocarbonylimidazole,[105,108] thioformates[109] and phenoxythionocarbonate[110] have also been shown to undergo the above transformation. Application of such a reaction to the alcohol **16** derived from **11** should, in principle, provide the required compund **14**.

Thus, the keto ester **11** in methanol was treated with sodium borohydride to yield compound **16** in 90% yield. The ir spectrum displayed a band at 3444 $cm^{-1}$ due to the hydroxyl group and another at 1735 $cm^{-1}$ due to the ester. The $^1$Hmr spectrum showed a broad singlet at $\delta$5.26 for the vinylic proton. A multiplet at $\delta$3.90 was assigned to the methine proton adjacent to the hydroxyl group. Three singlets at $\delta$3.72, 0.92, and 0.82 were attributed to the ester methyl and the _gem_-dimethyl groups respectively. The vinylic methyl group appeared at $\delta$1.68. The mass spectrum displayed a molecular ion peak at m/e 252.1729 indicating the chemical formula $C_{15}H_{24}O_3$.

When the alcohol **16** was treated with sodium hydride and carbon disulfide in 1,2-dimethoxyethane at room temperature followed by addition of methyl iodide, the S-methyl xanthate **17** was furnished as the reaction product in 95% yield. In the ir spectrum, bands at 1737 and 1054 $cm^{-1}$ were attributed to the ester and xanthate functionalities respectively. The $^1$Hmr spectrum showed a doublet of doublets (J = 12, J' = 4 Hz) at δ6.20 which was assigned to the proton adjacent to the xanthate group. A singlet at δ2.54 was assigned to the S-methyl group of the xanthate and a broad singlet at δ1.72 to the vinylic methyl group. The mass spectrum showed a molecular ion peak at m/e 342.1319 due to the chemical formula $C_{17}H_{26}O_3S_2$. The xanthate **17** was then heated with tri-n-butylstanne and a catalytic amount of 2,2'-azobis[2-methyl-2-propionitrile] in toluene at reflux overnight to give the ester **14** in 90% yield.

Having improved the yield of **14**, we were ready at this point to modify the angular ester function to the isoacanthodoral (**2**) carbon framework. The ester was to be converted to the aldehyde **18**, which would then be extended by one carbon to give the compound **7**. To convert the ester **14** to the aldehyde **18**, the use of diisobutylaluminum hydride[111] was anticipated since it is known to convert esters directly to aldehydes. However, the starting



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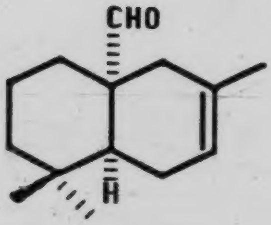

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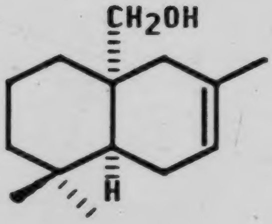

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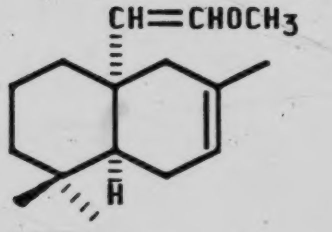

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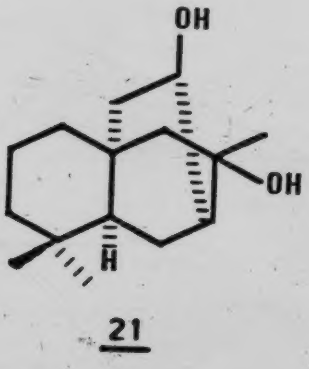

21

material was recovered intact upon treatment of the ester **14** with diisobutylaluminum hydride in toluene at -78°C. When the reaction was carried out at room temperature only 20% yield of alcohol **19** was obtained. It was therefore decided to convert the ester to the alcohol **19** first and then oxidize it to the aldehyde **18**. Upon treatment of the ester **14** with sodium bis(2-methoxyethoxy)aluminum hydride[112] in toluene at 0°C, it was converted to the alcohol **19** in 98% yield in 30 min. The ir spectrum showed a band at 3320 $cm^{-1}$ due to the hydroxyl group. The $^1$Hmr spectrum exhibited a broad singlet at $\delta$5.30 which was assigned to the vinylic proton. The methylene protons adjacent to the hydroxyl group displayed an AB pattern ($J = 10$ Hz each) at $\delta$3.38 and 3.24. A broad singlet at $\delta$1.64 was assigned to the vinylic methyl group. Two methyl singlets were observed at $\delta$0.92 and 0.82. The mass spectrum showed, a molecular ion peak at m/e 208.1829 for the chemical formula $C_{14}H_{24}O$. Swern's oxidation[113] was used to convert the alcohol to an aldehyde. Thus, upon treatment with a mixture of dimethyl sulfoxide and oxalyl chloride followed by triethylamine, the alcohol **19** was converted to the aldehyde **18** in 80% yield. The ir spectrum exhibited bands at 1724, 2800, and 2780 $cm^{-1}$ for an aldehyde. The $^1$Hmr spectrum showed a singlet at $\delta$9.34 which confirmed the presence of an aldehyde. Two broad singlets at δ5.32 and 1.68 were assigned to the vinylic proton and methyl group respectively. Two other methyl singlets were observed at δ0.96 and 0.84. The mass spectrum exhibited a molecular ion peak at m/e 206.1670 for the chemical formula $C_{14}H_{22}O$.

Elaboration of the aldehyde **18** to the compound **7** required the extention of the aldehyde function by one carbon. Of the options available,[114-116] the Wittig reaction[114] was chosen for its mildness and simplicity. The aldehyde **18** was therefore added to the (methoxymethyl)triphenylphosphorane ylide in benzene to give a 2:1 mixture of _trans_ and _cis_ enol ether **20** in 46% yield. The ir spectrum displayed bands at 1650 $cm^{-1}$ for the trisubstituted double bond and 1204 $cm^{-1}$ for the enol ether. The $^1$Hmr spectrum exhibited two doublets at δ6.18 (J = 12 Hz) and δ5.66 (J = 6 Hz) for the proton α to the methoxy group in the _trans_ and _cis_ compounds respectively. The other proton of the enol ether appeared as two doublets at δ4.78 (J = 12 Hz) and δ4.24 (J = 6 Hz). The methoxy group appeared as two singlets at δ3.56 and 3.50. Three singlets at δ1.70, 0.90, and 0.82 were assigned to the vinylic and _gem_-dimethyl methyl groups. The mass spectrum displayed a molecular ion peak at m/e 234.1995 for the chemical formula $C_{16}H_{26}O$.

All that was needed at this stage was the conversion of the enol ether to an aldehyde. Upon exposure of the enol ether **20** to 5 N hydrochloric acid or 30% perchloric acid [117] the product obtained showed an ir absorption band at 3400 $cm^{-1}$ due to a hydroxyl group. The $^1$Hmr spectrum displayed a multiplet at $\delta$ 4.60 which was assigned to a methine proton adjacent to a hydroxyl group. Three methyl singlets were observed at $\delta$ 1.64, 1.45 and 1.06. The mass spectrum showed a molecular ion peak at m/e 250.1932 for the chemical formula $C_{16}H_{26}O_2$. The foregoing spectral data suggested that the product obtained could be the compound **21**, the Prins reaction product.

The double bond in **20** was therefore involved in a reaction under the aqueous acid conditions. Since the double bond was required to remain intact for a successful synthesis of **7**, other alternatives were explored.[118-122] It was recognized that the hydrolysis should be done in the absence of aqueous acids. When boron tribromide[118] was used, unidentifiable products were obtained. The starting material was recovered intact when the enol ether **20** was exposed to demethylating conditions with chlorotrimethylsilane[119] and sodium iodide in acetonitrile. With the use of other demethylating agents such as phenylphosphonodichloridate[120] and sodium iodide, sodium ethylthiolate,[121] and lithium diphenylphosphide,[122] the starting material was also recovered intact.

From the above discussion, it could be concluded that the intermediate of the type **20** which would require aqueous acid hydrolysis to the **7** was not suitable for the present synthesis. To circumvent this, a Wittig reagent such as the (benzyloxymethyl)triphenylphosphorane ylide could be used and the resulting enol ether converted to the required aldehyde by either a dissolving metal reaction or hydrogenolysis without affecting the isolated double bond. Studies towards this end are currently under investigation.

# EXPERIMENTAL

## General

For general remarks see Chapter I of this thesis.

## Materials

Boron trifluoride etherate was distilled over calcium hydride according to the procedure of Brown.[85,123] Argon and solvents used were purified as described in Chapter I of this thesis.

## (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]-deca-3,8-dien-2-one (**9**) and (1R*,6S*)-1-Carbomethoxy-5,5,8-trimethylbicyclo[4.4.0]deca-3,8-dien-2-one (**10**)

To a solution of **8** (7 g, 0.039 mol) and isoprene (77.8 mL, 0.78 mol) in ether (280 mL) at 0°C, was added boron trifluoride etherate (2.4 mL, 0.02 mol). The reaction mixture was stirred at 0°C for 48 h under argon atmosphere. Saturated aqueous sodium bicarbonate (140 mL) was added and the resulting solution was extracted with ether. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue on silica gel with 10-12% ether in petroleum-ether gave a 70:30 mixture ($^1$Hmr analysis) of keto esters **9** and **10** (9.1 g, 94% yield). The mixture was dissolved in hot ether and seeded with pure crystals of **9** (obtained by preparative high pressure liquid chromatography on a Waters Associates Prep LC/System 500 using one silica gel cartridge and eluting with 5% ethyl acetate in n-hexane) to give 3 g of compound **9**: m.p. 94-96°C; ir 1745, 1731 (ester C=O), 1675 (enone C=O), 1380, and 1365 cm$^{-1}$ ($CH_3$); $^1$Hmr $\delta$6.64 (d, 1H, J = 9 Hz, -CH=CHCO-), 5.94 (d, 1H, J = 9 Hz, -CH=CHCO-), 5.39 (m, 1H, =CH-), 3.74 (s, 3H, $-OCH_3$), 2.72 (ddd, 1H, J = 6.5 Hz, J' = 3 Hz, J" = 0.5 Hz, C-10H) 2.54 (d, 1H, J = 16 Hz, C-8H), 2.18 (d, 1H, J = 16 Hz, C-8H), 2.11 (br s, 2H, C-5 $-CH_2-$), 1.7 (br s, 3H, $=\overset{|}{C}CH_3$), 1.24 (s, 3H, $-CH_3$) and 1.06 (s, 3H, $-CH_3$); $^{13}$Cmr $\delta$197.3 (C-1), 172.8 ($-CO_2-$), 157.8 (C-3), 131.1 (C-7), 123.9 (C-2), 119.1 (C-6), 57.4 (C-9), 52.3 ($-OCH_3$), 40.3 (C-10), 35.9 (C-4), 33.0 (C-8), 30.4 (C-4 $CH_3$), 24.2 (C-5), 23.5 (C-4 or C-7 $CH_3$) and 23.4 (C-4 or C-7 $CH_3$); ms M$^+$ 248.2410 (calcd. for $C_{15}H_{20}O_3$: 248.1410). Anal. calcd. $C_{15}H_{20}O_3$: C, 72.55, H, 8.12; found: C, 72.43, H, 8.03.

The minor regio-isomer obtained from the high pressure liquid chromatography, after two recrystallizations from ether gave colorless rhombs of pure keto ester **10**: m.p. 91-93°C; ir 1741 (ester C=O), 1668 (enone C=O), 1372 ($CH_3$), and 825 cm$^{-1}$ (C=C); $^1$Hmr $\delta$6.6 (d, 1H, J = 9

Hz, $-C\underline{H}=CHCO-$), 5.94 (d, 1H, J = 9 Hz, $-CH=C\underline{H}CO-$), 5.44 (br s, 1H, $=CH-$), 3.74 (s, 3H, $-OCH_3$), 2.79 (dd, 1H, J = 7 Hz, J' = 3 Hz, C-10), 2.7 (dm, 1H, J = 17 Hz, C-8), 1.68 (br s, 3H, $=\overset{|}{C}-CH_3$), 1.2 (s, 3H, $-CH_3$), and 1.04 (s, 3H, $-CH_3$); $^{13}$Cmr $\delta$197.6 (C-1), 172.9 ($-CO_2-$), 157.7 (C-3), 132.1 (C-6), 123.8 (C-2), 118.4 (C-7), 56.5 (C-9), 52.3 ($-OCH_3$), 41.2 (C-10), 36.1 (C-4), 30.3 (C-4 $CH_3$), 28.9 (C-5 or C-8), 28.6 (C-5 or C-8), 23.5 (C-4 or C-6 $CH_3$), and 23.4 (C-4 or C-6 $CH_3$); ms $M^+$ 248.1419 (calcd. for $C_{15}H_{20}O_3$ 248.1410).

## (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethyl-2-triethylsiloxybicyclo[4.4.0]deca-2,8-diene (**12**)

Finely divided keto ester **9** (2.14 g, 8.62 mmol) was suspended in triethylsilane (1.99 g, 17.24 mmol) and tris-triphenylphosphine rhodium (I) chloride (39.4 mg, 0.0422 mmol) was added. The mixture was stirred for 5 h, after which additional triethylsilane (1.99 g) was added. After being stirred for a additional 19 h, the mixture was diluted with petroleum ether, filtered and concentrated to give crude silyl enol ether **12** (3.5 g). Column chromatography on silica gel with 5% ether in petroleum ether gave pure **12** (3.0 g, 96% yield) as a colorless oil: ir 1743, 1729 (C=O), 1674 (enol C=C), 1390, 1378, 1364

($CH_3$), and 824 $cm^{-1}$ (C=C); $^1$Hmr $\delta$5.26 (m, 1H, $CH_3\overset{|}{C}=CH-$), 4.65 (dd, 1H, J = 6 Hz, J' = 3 Hz, $-O\overset{|}{C}=CH-$), 3.65 (s, 3H, $-OCH_3$), 2.66 (dd, 1H, J = J' = 8 Hz, $-\overset{|}{C}H-$), 1.66 (bs, 3H, $=\overset{|}{C}CH_3$), 0.98 (s, 6H, $-\overset{|}{C}(CH_3)_2$), 0.96 (t, 9H, J = 8 Hz, $-Si(CH_2\underline{CH_3})_3$), 0.70 (q, 6H, J = 8 Hz, $-Si(C\underline{H_2}CH_3)_3$); ms $M^+$ 364.2436 (calcd. for $C_{21}H_{36}O_3Si$: 364.2433); Anal. calcd. for $C_{21}H_{36}O_3Si$: C, 69.24; H, 9.96; found: C, 69.04, H, 9.79.

### (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]-deca-8-en-2-one (**11**)

Pure silyl enol ether **12** (3.75 g, 0.01 mol) was dissolved in methanol (180 mL) and a solution of 10% aqueous potassium carbonate (40 mL) was added. The mixture was stirred for 4 h then poured into water and extracted with dichloromethane. The extracts were washed with water, dried, filtered and concentrated. Column chromatography of the residue, eluting with 3-10% ether in petroleum ether, gave keto-ester **11** (2.15 g, 90% yield) as a colorless oil: ir 1743, 1731 (ester C=O), 1712 (ketone C=O) and 1430 $cm^{-1}$ ($-CH_2-C=O$); $^1$Hmr $\delta$5.40 (br s, 1H, =CH-), 3.72 (s, 3H, $-OCH_3$), 1.65 (br s, 3H, $=\overset{|}{C}CH_3$), 1.00 (s, 3H, $CH_3$) and 0.9 (s, 3H, $CH_3$); ms $M^+$ 250.1567 (calcd.

for $C_{15}H_{22}O_3$: 250.1569). Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; Found: C, 72.09, H, 8.91.

(1R*,6S*)-1-Carbomethoxy-2,2-ethylenedithio-5,5,9-trimethylbicyclo[4.4.0]dec-8-ene **(13)**

Keto ester **11** (103 mg, 0.4 mmol) was dissolved in 1,2-ethanedithiol (1 mL, 11.9 mmol). The solution was chilled to 0°C and boron trifluoride etherate (126 mg, 0.089 mmol) was added. The mixture was stirred under an argon atmosphere at room temperature for 1 h. The reaction mixture was poured into an ice-cold 2 N aqueous sodium hydroxide (3 mL), and extracted with chloroform (4 x 5 mL). Drying the extracts over magnesium sulphate, filtration, and concentration gave the crude product which was purified by column chromatography on silica gel. Elution with 2% ethyl acetate in petroleum ether gave the ester **13** (119 mg, 91% yield): ir 1740 $cm^{-1}$ (ester C=O); $^1$Hmr $\delta$ 5.26 (m, 1H, =CH-), 3.66 (s, 3H, $-OCH_3$), 3.14 (m, 1H, $-SCH_2CH_2S-$), 1.62 (br s, 3H, $=\overset{|}{C}CH_3$), 0.96 (s, 3H, $-CH_3$), and 0.84 (s, 3H, $-CH_3$); ms $M^+$ 326.1369 (calcd. for $C_{17}H_{26}O_2S_2$: 326.1376).

### (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo-[4.4.0]dec-8-en-2-ol (**16**)

The keto ester **11** (2.3 g, 0.009 mol) was dissolved in methanol (20 mL) and the resulting solution was stirred and chilled to 0°C in an ice bath. Solid sodium borohydride (0.6 g, 0.016 mol) was added in small portions. The reaction mixture was stirred for 45 min at 0°C. Saturated aqueous ammonium chloride was added to the mixture and was extracted with dichloromethane. The organic extracts were washed with brine solution, dried over magnesium sulphate, filtered, and concentrated. The residue obtained was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in petroleum ether, to give the alcohol **16** (2.08 g, 90% yield): ir 3444 (O-H) and 1735 $cm^{-1}$ (ester C=O); $^1$Hmr $\delta$5.26 (br s, 1H, =CH-), 3.9 (m, 1H, -$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$-OH), 3.72 (s, 3H, -$OCH_3$), 1.68 (br s, 3H, =$\overset{|}{\mathrm{C}}$-$CH_3$) 0.92 (s, 3H, -$CH_3$) and 0.82 (s, 3H, -$CH_3$); ms $M^+$ 252.1729 (calcd. for $C_{15}H_{24}O_3$: 252.1726).

### (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethyl-2-(methylmercaptothiocarbonyloxy)bicyclo[4.4.0]dec-8-ene (**17**)

A solution of the alcohol **16** (296 mg, 1.17 mmol) in 1,2 dimethoxyethane (5 mL) at 0°C was treated with sodium hydride (80% dispersion in mineral oil; 140 mg, 5.85

mmol). After stirring for 20 min, this solution was treated with carbon disulfide (334 mg, 11.7 mmol) followed by methyl iodide (830 mg, 5.85 mmol) and the resulting light brown solution was stirred at room temperature for 8 h under an argon atmosphere. The reaction mixture was then poured into ice-cold water and extracted with ether. The ether extracts were washed with water and saturated brine soltuion. The combined extracts were dried over anhydrous sodium sulfate and concentrated. Chromatography on silica gel column, eluting with 2-5% ethyl acetate in petroleum ether, gave the xanthate **17** (382 mg, 95% yield): ir 1737 (ester C=O) and 1054 $cm^{-1}$ (C=S); $^1$Hmr $\delta$ 6.2 (dd, 1H, J = 12 Hz, J' = 4 Hz, $-\overset{|}{C}HOCS-$), 5.34 (br s, 1H, =CH-), 3.66 (s, 3H, $-OCH_3$), 2.54 (s, 3H, $-SCH_3$), 1.72 (br s, 3H, $=\overset{|}{C}-CH_3$), 0.98 (s, 3H, $-CH_3$), and 0.86 (s, 3H, $-CH_3$); ms $M^+$ 342.0519 (calcd. for $C_{17}H_{26}O_3S_2$: 342.0525).

## (1R*,6S*)-1-Carbomethoxy-5,5,9-trimethylbicyclo[4.4.0]dec-8-ene **14**

### (i) From thioketal **13**

To a solution of the thioketal (402 mg, 1.23 mmol) in dry benzene (20 mL), freshly prepared Raney Nickel (W-2, 3.9 mL) was added. The solution was stirred at room temperature under an argon atmosphere for 7 h. The mixture was then filtered and the residue was washed successively with benzene, ethanol and ethyl acetate. The filtrates were concentrated. Flash column chromatography of the combined residue on silica gel, eluting with 2% ethyl acetate in petroleum ether, afford the ester **14** (123 mg, 42%); 1729 $cm^{-1}$ (ester C=O): $^1$Hmr $\delta$5.26 (m, 1H, =CH-), 3.62 (s, 3H, $-OCH_3$), 1.62 (br s, 3H, $=\overset{|}{C}-CH_3$), 0.94 (s, 3H, $-CH_3$) and 0.84 (s, 3H, $-CH_3$); ms m/e 236.1768 (calcd. for $C_{15}H_{24}O_2$: 236.1777).

Further elution gave a mixture of the ester **17** and diene **18** (78 mg, 27% yield) followed by diene **18** (53 mg, 18% yield): 1730 $cm^{-1}$ (ester); $^1$Hmr $\delta$5.66 (dt, 1H, J = 10 Hz, J' = 4 Hz, -CH=), 5.6 (dt, 1H, J = 10 Hz, J' = 1 Hz, =CH-) and 5.36 (m, 1H, =CH-); ms $M^+$ 234.1614 (calcd. for $C_{15}H_{22}O_2$: 234.1621).

### (ii) From Xanthate 17

The thionocarbonate derivative **17** (540 mg, 1.58 mmol), tri-n-butyltin hydride (690 mg, 2.37 mmol) and 2,2'-azobis(2-methyl-2-propionitrile) (0.011 g) were dissolved in toluene (20 mL). The resulting solution was deaerated by bubbling argon through it for 20 min. The deaerated solution was refluxed under the argon atmosphere overnight. The color of the solution changing from deep red to colorless. The reaction mixture, after cooling to room temperature, was concentrated. Purification by column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether, gave the ester **14** (335 mg, 90% yield).

### (1R*,6S*)-1-Hydroxymethyl-5,5,9-trimethylbicyclo-[4.4.0]dec-8-ene (**19**)

The stirred solution of the ester **14** (51 mg, 0.27 mmol) in toluene (2 mL) cooled to 0°C was treated with a solution of sodium bis-(2-methoxyethoxy)aluminum hydride (0.5 mL of 3.4 M, 0.5 mmol) in toluene. The resulting mixture was stirred under an argon atmosphere for 30 min at 0°C. The solvent was removed under reduced pressure and the residue was treated with a saturated solution of ammonium chloride. The precipitate was filtered and thoroughly washed with ether. The combined organic filtrate was washed with water and saturated brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated. The compound obtained was purified on silica gel column, eluting with 20% ethyl acetate in petroleum ether, to give the alcohol **19** (44 mg, 98% yield): ir 3320 cm$^{-1}$ (-OH); $^1$Hmr δ5.3 (br s, 1H,

=CH-), 3.38, 3.24 (both d, 2H, J = 10 Hz each, $-CH_2OH$), 1.64 (br s, 1H, $=\overset{|}{C}CH_3$), 0.92 (s, 3H, $-CH_3$), and 0.82 (s, 3H, $-CH_3$); ms M$^+$ 208.1829 (calcd. for $C_{14}H_{24}O$: 208.1828).

### (1R*,6S*)-1-Formyl-5,5,9-trimethylbicyclo[4.4.0]dec-8-ene (18)

A solution of dichloromethane (3 mL) and oxalyl chloride (0.11 mL, 1.16 mmol) was placed in a 25 mL round-bottomed flask at -78°C. Dimethyl sulfoxide (0.18 mL, 2.32 mmol) in dichloromethane (0.5 mL) was added to the stirred oxalyl chloride solution at -60°C. The reaction mixture was stirred for 2 min and the alcohol **19** (220 mg, 1.06 mmol) in dichloromethane (1 mL) was added in a dropwise fashion via syringe. Stirring was continued for another 30 min. Triethylamine (0.74 mL, 5.3 mmol) was added and the mixture was stirred for 10 min and then allowed to warm to room temperature. Water (5 mL) was added and the aqueous layer was extracted with additional dichloromethane (3 x 5 mL). The organic layers were combined, washed with saturated brine solution, dried over anhydrous magnesium sulphate, filtered and concentrated. Flash column chromatography on silica gel, eluting with 5% ethyl acetate in petroleum ether gave the aldehyde **18** (174 mg, 80% yield): ir 1724 (aldehyde C=O), 2800 and 2780

$cm^{-1}$ (aldehyde C-H); $^1$Hmr $\delta$ 9.34 (s, 1H, -CHO), 5.32 (br s, 1H, =CH-), 1.68 (br s, 3H, $=\overset{|}{C}CH_3$), 0.96 (s, 3H, $-CH_3$) and 0.84 (s, 3H, $-CH_3$); ms $M^+$ 206.1670 (calcd. for $C_{14}H_{22}O$: 206.1672).

## (1R*,6S*)-1-(2-Methoxyethenyl)-3,7,7-trimethylbicyclo-[4.4.0]dec-3-ene (20)

A mixture of sodium hydride (121 mg of 50% dispersion in oil; 2.5 mmol) in dimethyl sulfoxide (2 mL) and benzene (3 mL) was heated at 90°C, under an argon atmosphere, for 45 min, to produce the methylsulfinyl carbanion. After allowing the mixture to come to room temperature, (methoxymethyl)triphenylphosphonium chloride (922 mg, 2.73 mmol) was added and the mixture stirred for 20 min. To the deep red solution produced, the aldehyde **18** (193 mg, 0.94 mmol) was added. After stirring the mixture overnight, it was poured into ice water (10 mL) and extracted with ether (4 x 10 mL). The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated. The residue was distilled at 60°C/2.5 torr to remove triphenylphosphine oxide. The distillate was purified by column chromatography on silica gel, using 1% ethyl acetate in petroleum ether. The product **20** (101 mg, 46% yield) was a mixture of the cis and trans isomers which showed the following spectral characteristics: ir 1650 (olefin) and 1204 $cm^{-1}$ (vinyl ether); $^1$Hmr $\delta$ 6.18; 5.66 (d, 2/3H, J = 12 Hz; d, 1/3H, J = 6 Hz, $-CH=C\underline{H}OCH_3$), 4.78; 4.24 (d, 2/3H, J = 12 Hz; d, 1/3H, J = 6 Hz, $-\underline{CH}=CHOCH_3$), 3.56, 3.50 (both s, 3H, $-CH=CHOC\underline{H_3}$), 1.70 (br s, 3H, $CH_3C=$), 0.90 (s, 3H, $-CH_3$), and 0.82 (s, 3H, $-CH_3$); ms $M^+$ 234.1995 (calcd. for $C_{16}H_{26}O$: 234.1985).

## 2,12-Dihydroxy-8,8,12-trimethyltricyclo[6.2.2.0$^{4,9}$]-dodecane (21)

To the enol ether **20** (21 mg, 0.09 mmol) in tetrahydrofuran (1 mL) at 0°C was added 30% perchloric acid (0.01 mL, 0.17 mmol) and stirred under an argon atmosphere for 10 min. The mixture was then neutralized with ice cold saturated aqueous sodium bicarbonate solution and extracted with ether (3 x 5 mL). The organic extracts were washed with water, dried over magnesium sulfate, filtered, and concentrated. Column chromatography of the resulting residue on silica gel, eluting with 20% ethyl acetate in petroleum ether, gave **21** (18 mg, 82% yield): ir 3400 $cm^{-1}$ (OH); $^1$Hmr $\delta$ 4.60 (m, 1H, $-\overset{|}{C}\underline{H}OH$), 1.60 (s, 3H, $HO\overset{|}{C}C\underline{H_3}$), 1.40 and 1.06 (both s, 3H each, 2 x $CH_3$); ms $M^+$ 250.1932 (calcd. for $C_{16}H_{26}O_2$: 250.1970).

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